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DRINKING WATER HEALTH DOCUMENT ON 2,4,5-TP (SILVEX)

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DRINKING WATER CRITERIA DOCUMENT FOR 2(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID (2,4,5-TP)

Prepared for

OFFICE OF DRINKING WATER

Prepared by

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The Office of Drinking Water (ODW), Environmental Protection Agency has prepared a Drinking Water Criteria Document on 2,4,5-TP (Silvex). This Criteria Document is an extensive review of the following topics:

- Physical chemical properties of 2,4,5-TP (Silvex)
- Toxicokinetics and human exposure to 2,4,5-TP (Silvex)
- Health Effects of 2,4,5-TP (Silvex) in humans and animals
- Mechanisms of toxicological effect of 2,4,5-TP (Silvex)
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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1985; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
a.e.	Acid equivalent
bw	Body weight
CNS	Central nervous system
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DWEL	Drinking Water Equivalent Level
ED_{50}	Median effective dose
HA	Health Advisory
i.v.	Intravenous
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RfD	Reference Dose
RNA	Ribonucleic acid
s.c.	Subcutaneous
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
2,4,5-T	2,4,5-Trichlorophenoxy acetic acid
2,4,5-TP	2,4,5-Trichlorophenoxypropionic acid
TWA	Time weighted average
UV	Ultraviolet

I. SUMMARY

2,4,5-Trichlorophenoxypropionic acid (2,4,5-TP) is a commonly used systemic herbicide for both agricultural and nonagricultural purposes. The commercial herbicide is contaminated with 2,3,7,8-TCDD, a highly toxic tetra-chlorinated dibenzo-p-dioxin.

In the early 1960s, the TCDD contaminant level in commercial 2,4,5-T and 2,4,5-trichlorophenol ranged from 5-50 ppm, while by the early 1970s manufacturers set a limit of 0.1 ppm TCDD contamination. Since 2,4,5-TP is derived from 2,4,5-T and trichlorophenol, the TCDD contaminants would be assumed to occur in 2,4,5-TP. The use of such contaminated products in toxicity testing may affect both the qualitative and quantitative interpretation of results as related to 2,4,5-TP. The toxicokinetic profile of 2,4,5-TP indicates that this compound is rapidly and extensively absorbed by mammals following oral exposure and, by analogy to 2,4,5-T, would be anticipated to have a high degree of binding to plasma protein and tissue. Excretion of the parent compound suggests that 2,4,5-TP is not metabolized extensively by rats. Renal excretion is rapid and is the predominant route of excretion.

Acute oral exposure to 2,4,5-TP causes a variety of physiological (muscular weakness, depression) and biochemical (increased SGPT and SGOT) effects on mammals. The liver and kidney appear to be the target organs following prolonged exposure to this compound.

2,4,5-TP has been found to cause teratogenic effects in both mice and rats. Although contamination of 2,4,5-TP by 2,3,7,8-TCDD may contribute to the teratogenic and reproductive effects of this compound, the extent of this contamination is unclear.

Animal studies to evaluate the carcinogenic potential of 2,4,5-TP do not report significant increases in tumors; however, these studies are inadequate because significant study design weaknesses preclude the proper evaluation of carcinogenic potential. Only limited mutagenicity testing has occurred with Ames assays showing no response. Human studies show some positive evidence that exposure to phenoxy herbicides together with 2,3,7,8-TCDD as a contaminant correlates with an increase in soft tissue sarcomas and non-Hodgkins lymphomas. The U.S. EPA has given this mixture of compounds a B1 weight-of-evidence ranking, which indicates that this mixture is probably carcinogenic for humans. Neither 2,4,5-TP nor 2,3,7,8-TCDD alone can, at present, be shown to have this carcinogenic potential, however. This situation equates to a weight-of-evidence classification of Group D using U.S. EPA's Carcinogen Risk Assessment Guidelines. Group D means that the data is inadequate to determine the positive or negative potential for carcinogenicity. However, the presence of a 2,3,7,8-TCDD contaminant in 2,4,5-TP (which was common in the 1960s at a level as high as 5-50 ppm, more recently in the 1970s reduced to 0.1 ppm) gives rise for concern about the possible carcinogenicity of such a mixture. Given that 2,3,7,8-TCDD is considered a probable human carcinogen, Group B2, exposure to 2,4,5-TP with a hazardous level of TCDD as a contaminant would probably incur a carcinogenic risk.

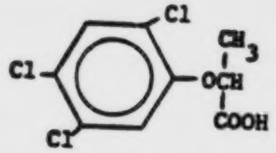
The quantification of toxicological effects of 2,4,5-TP involved the identification of doses at which adverse health effects are anticipated for both chronic and acute exposures for adults and children consuming 2 ℓ or 1 ℓ water/day, respectively. The 10-day HA of 0.2 mg/ℓ (1.4 mg/day) was derived for a child exposed to 2,4,5-TP in water. A DWEL of 0.26 mg/ℓ was derived for lifetime exposure for an adult. Pertinent data regarding the effects on animals or humans as a result of acute exposure to 2,4,5-TP could not be located in the available literature; therefore, no 1-day HA could be derived. Similarly, due to non-availability of any suitable data longer-term HAs could also not be determined. However, it is recommended that the DWEL, adjusted for a 10-kg child (0.07 mg/ℓ) be used as a conservative estimate of a longer-term HA. The concern for carcinogenic hazards is on a case-by-case situation depending upon TCDD contamination as previously discussed.

The U.S. EPA has taken significant regulatory action on 2,4,5-TP as a herbicide product. As of February 1987 the result of the actions taken should be to reduce the availability of 2,4,5-TP and hence its discharge to the environment to virtually a nil level. The exception to this would be a situation where storage of 2,4,5-TP in controlled or uncontrolled dump sites or related scenarios might result in a discharge to the environment. The regulatory action against herbicide uses began in February 1979 when 2,4,5-TP use in forestry, rights of way, pasture, home and garden, and ornamental gardening was suspended. Between 1979 and February 1985 all other registrations for 2,4,5-TP uses were cancelled by the U.S. EPA. From February 1985 through February 1986, existing 2,4,5-TP stockpiles only were allowed into commerce for highly limited use. As of February 1986 all sale of 2,4,5-TP ceased.

Structures, Molecular Weights and Synonyms

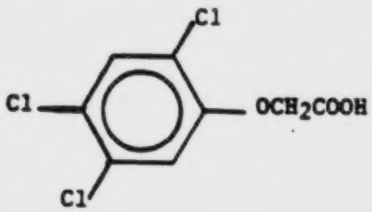
Since 2,4,5-T will be discussed for comparison purposes in some of the sections to follow, its physical and chemical properties will be presented here along with those of 2,4,5-TP.

2(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP), Silvex, Fenoprop



Molecular weight: 269.5

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)



Molecular weight: 255.5

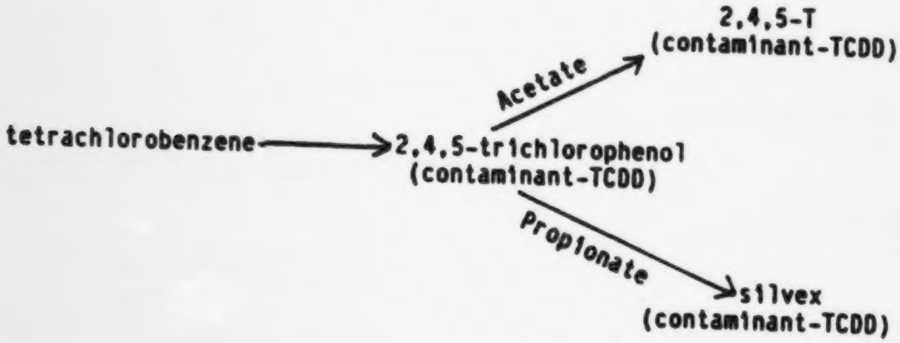
Chemical Abstract Service (CAS) Number and Registry of Toxic Effects of Chemical Substances (RTECS) Number

2,4,5-TP CAS Number:	93-72-1
RTECS Number:	UF8225000
2,4,5-T CAS Number:	93-765
RTECS Number:	AJ8400000

Formulation of 2,4,5-TP (Silvex)

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is an extremely toxic contaminant that forms when tetrachlorobenzene is hydrolyzed in an alkaline ethylene glycol solution to produce 2,4,5-trichlorophenol. The amount of TCDD produced increases with increases in the temperature of the reaction. The 2,4,5-trichlorophenol is used as an intermediary in the production of (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T) and (2,4,5-trichlorophenoxy)-propionic acid (2,4,5-TP, silvex). Therefore, the TCDD contaminates both products to the same extent (see figure below).

TCDD can also occur in other chlorinated phenols and in the chemicals synthesized from them. TCDD does not occur naturally in the environment, but exists only as a contaminant of other chemicals.


2,4,5-T
(contaminant-TCDD)
Acetate
tetrachlorobenzene
2,4,5-trichlorophenol
(contaminant-TCDD)
Propionate
silvex
(contaminant-TCDD)

In the 1960s, the TCDD content in commercial 2,4,5-T and 2,4,5-trichlorophenol ranged from 5-50 ppm. By the early 1970s, the manufacturers had set a limit of 0.1 ppm TCDD contamination in their products.

Chemical/Physical Characteristics (taken from Weed Science Society of America, 1979, unless otherwise stated)

2(2,4,5-Trichlorophenoxy)propionic acid (2,4,5-TP) is a white powder used to control woody plants, broadleaf herbaceous weeds and aquatic weeds. It is also used as a selective postemergence herbicide in rice farming and in sugarcane production; it controls weeds not susceptible to 2,4-dichlorophenoxyacetic acid (2,4-D).

Melting point:	178.2°C
Specific gravity:	Powder density (at 30°C) 1.640 bulk density, 27.4 lb/cu. ft.
Solubility in water:	140 ppm at 25°C
pK_a:	2.83 (Cessna and Grover, 1978)
Solubility in carbon tetrachloride:	860 ppm at 26°C Ester formulations are highly soluble in petroleum derivative solvents and are only slightly soluble in water (usual carrier: oil and oil-water mixture).
Spectroscopic data:	UV absorption maximum 209, 287, 295 (NRCC, 1978) IR absorption bands in cm^{-1} 815, 863 (NRCC, 1978)
Commercial synthesis:	Reaction of 2,4,5-trichlorophenol with methyl ester of alpha-chloropropionic acid in the presence of methanol and sodium methoxide and acidification of the product (Esposito et al., 1980). Reactivity: should react with organic and inorganic bases to form salts and with alcohols to form esters.

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), when pure, is a white crystaline solid. As a systemic herbicide, it is used for both agricultural and nonagricultural purposes. The three commonly used application techniques for this herbicide are aerial application, ground application and injection on basal application (Norris, 1980).

Melting Point:	154-155°C More than 400 formulated pesticide products in the market contain the salts of ester forms of 2,4,5-T as active ingredients (Esposito et al., 1980). The commercial products of 2,4,5-T are used as cropland weed control (i.e., in rice fields) and in noncropland weed control (i.e., for aquatic and broadleaf weeds) in the control of woody plants and rights of ways, and in the management of forests, pastures, fallow and rangelands (Ramanujam, 1981).
Decomposition temperature:	Probably >200°C; stable at its melting point
Specific Gravity:	1.662 at 30°C
Vapor Pressure:	6.46×10^{-6} (25°C) (Khan, 1985)
Solubility:	
Water:	237 ppm at 30°C; 189 ppm at 20°C (NRCC, 1978).
Ethanol:	548 g/ℓ (NRCC, 1978) Amine salts are soluble in water and slightly soluble in petroleum oils; esters are slightly soluble in water and soluble in petroleum oils (usual carrier: water, oil or oil-water emulsion).
Spectroscopic data:	Ultraviolet absorption maxima in nm: 207, 289 and 297 Infrared absorption bands cm^{-1}: 764, 680
Commercial Synthesis:	Reaction of 2,4,5-trichlorophenol with monochloroacetic acid under alkaline conditions.
Reactivity:	Reacts with organic and inorganic bases to form salts and with alcohols to form esters (IARC, 1977).

No analyses of 2,4,5-TP were found in the available literature; however, the impurities in 2,4,5-TP will probably be similar in nature to those in 2,4,5-T, since 2,4,5-trichlorophenol is the starting material for both products. The following list is an analysis for technical 2,4,5-T (Bovey, 1980). Whenever acetic acid derivatives are present, propionic acid derivatives would be expected in 2,4,5-TP. Impurities may vary among producers and among batches of the same producer (Bovey, 1980).

91.0 ± 1.0	2,4,5-T
0.5 ± 0.1	2,4,5-trichloroanisole
2.0 ± 0.5	5-methoxy(2,4-dichlorophenoxy)acetic acid
2.0 ± 0.5	2-methoxy-4,5-dichlorophenoxyacetic acid
0.3 ± 0.1	2,4,5-trichlorophenol
3.0 ± 0.5	bis-2,4,5-trichlorophenoxyacetic acid
0.3 ± 0.1	2,5-dichlorophenoxyacetic acid
0.2 ± 0.1	SO_4
0.2 ± 0.1	Sodium salt of 2,4,5-T
0.5 ± 0.2	H_2O
<0.1 ppm	2,3,7,8-tetrachlorodibenzo-_p_-dioxin (2,3,7,8-TCDD) required for registration of the product with the U.S. EPA.

Conversion factors for relating concentrations in air of some 2,4,5-TP esters are listed in Table II-1.

Summary

2(2,4,5-Trichlorphenoxy)propionic acid (mol. wt. 269.5), commonly known as 2,4,5-TP, is a white powder used as an herbicide. The pure compound has a melting point of 178.2°C, a specific gravity of 1.640 at 30°C, a water solubility of 140 ppm at 25°C and a carbon tetrachloride solubility of 860 ppm at 26°C. Esters of 2,4,5-TP are slightly water soluble but highly soluble in petroleum solvents. It is expected that the commercial product will have TCDD contamination depending on the maufacturing date. In the early 1970s the TCDD contaminant level was reduced to ≤0.01 ppm, whereas in the early 1960s the level was 5-50 ppm.

TABLE II-1

Conversion Factors for Some 2,4,5-TP Esters

Ester	Conversion Factors
methyl	1 ppm = 11.6 mg/m^3 1 mg/m^3 = 0.0859 ppm
ethyl	1 ppm = 12.2 mg/m^3 1 mg/m^3 = 0.0819 ppm
propyl (1- or 2-)	1 ppm = 12.8 mg/m^3 1 mg/m^3 = 0.0782 ppm
butyl	1 ppm = 13.4 mg/m^3 1 mg/m^3 = 0.0749 ppm
butoxy ethyl	1 ppm = 15.2 mg/m^3 1 mg/m^3 = 0.0660 ppm
propylene glycol butyl ether	1 ppm = 16.4 mg/m^3 1 mg/m^3 = 0.0610 ppm

III. TOXICOKINETICS

Limited data describing the toxicokinetic profile of 2,4,5-TP were located in the available literature. Review articles have been published on the fate of phenoxy acids in mammals (Gehring and Betso, 1978; Leng, 1977). Structural and metabolic considerations indicate that 2,4,5-T and 2,4,5-TP will probably behave similarly; therefore, some data on the toxicokinetics of 2,4,5-T are provided.

Animal Studies

Absorption. Ingestion of 2,4,5-TP and 2,4,5-T by mammals was followed by rapid and efficient absorption (up to 98-100% after small doses) from the gastrointestinal tract (Erne, 1966; NRCC, 1978). More than 90% of single oral doses of 2,4,5-T (0.17-41 mg/kg, given by Fang et al., 1973 or 100-200 mg/kg by Piper et al., 1973) were assimilated from the digestive tract of rats. Reabsorption of biliary-excreted 2,4,5-T was virtually complete (Eaton, 1982), which may contribute to a longer half-life and greater bioavailability.

The 2,4,5-T derived esters may be absorbed less readily than the acids and salts, by comparison with previous work with 2,4-D (2,4-dichlorophenoxyacetic acid) (Erne, 1966; NRCC, 1978). Rats given single doses of 100 mg/kg bw of the amine salt of 2,4-D by gavage had peak plasma levels (>100 μg/mℓ) in 7 hours, while a similar dose of the butyl ester resulted in maximum plasma levels of <50 μg/mℓ. In studies with 2,4-D, only the acid was detectable in the plasma or urine of rats, pigs and calves after an oral dose of the ester was administered, thus indicating that the ester undergoes hydrolysis. No data are available on the dermal or pulmonary absorption of 2,4,5-TP or 2,4,5-T in animals.

Distribution. Once the phenoxy acids are absorbed, they are rapidly distributed throughout the body. They are bound to plasma proteins, resulting in the retention in the plasma or extracellular compartments or both. Fang and Lindstrom (1980) reported that 2,4,5-T had the highest binding affinity to bovine serum albumin, *in vitro*, of several phenoxyacetic acids tested. There were two binding sites on the bovine serum albumin for 2,4,5-T and 2,4-D, while the other compounds had only one site. Senczuk and Pogorzelska (1981) reported in an abstract that 2,4,5-TP and 2,4,5-T blood levels remained high for 24-72 hours in rats treated with 50 mg of the compound.

Sauerhoff et al. (1977a) reported that a single i.v. dose of 5 or 50 mg/kg of ^{14}C-2,4,5-TP to rats resulted in greater concentrations of ^{14}C activity in the liver and kidney than in the fat, brain or muscle at 8 and 216 hours postadministration. Sauerhoff et al. (1976) indicated that the kidney tissue:blood concentration ratio was dose-dependent in the range of 5-100 mg/kg bw of 2,4,5-T administered intravenously to rats.

Small amounts of these herbicides were transferred to the young through the mother's milk after the dams received two doses of 0.17 mg/kg after giving birth (exact times not mentioned) (Fang et al., 1973). Pregnant mice were given i.v. injections of radiolabeled 2,4,5-T at various times during pregnancy and whole body autoradiography was performed at various times after injection (Lindquist and Ullberg, 1971). The visceral yolk sac epithelium of pregnant mice accumulated 2,4,5-T to a greater concentration than that found in blood; 2,4,5-T was gradually transferred to the fetus at late stages of pregnancy but without accumulation (Lindquist and Ullberg, 1971). Selective uptake of 2,4,5-T into the yolk sac epithelium and the absence of placental transfer in early pregnancy were effects similar to those seen with trypan blue in mouse embryos (Lloyd and Beck, 1969).

Metabolism and Excretion. Following gavage administration of a single 100 or 200 mg/kg bw dose of 2,4,5-T and subsequent absorption, 2,4,5-T was eliminated unchanged from the body predominantly (>93% in rats) through the urine (Piper et al., 1973). Only small amounts of 2,4,5-T were conjugated before excretion. Urinary excretion of ^{14}C-2,4,5-TP in rats accounts for 80.5 and 68.7% of the administered dose at 5 and 50 mg/kg levels, respectively (Sauerhoff et al., 1977a). Urinary excretion of low doses of 2,4,5-T (0.17 mg/kg bw) was normally rapid in adult animals (3.2-hour average half-life for elimination from blood in rats) but appeared to be extremely prolonged in neonates following exposure to an unquantified dose from the mother's milk (66-hour half-life for elimination from blood in rat pups) (Fang et al., 1973). This was perhaps due to the fact that in rats renal function is not complete for several weeks post partum. The fate of 2,4,5-T following a single oral administration of 5 mg/kg to rats and dogs revealed half-life values for 2,4,5-T clearance from plasma of 2.7 and 77.0 hours, respectively (Piper et al., 1973). The prolonged retention of 2,4,5-T in dogs provided a reasonable explanation for the generally observed greater toxicity of 2,4,5-T in dogs than in rats.

The possibility of cumulative or progressive inhibition of renal organic anion transport was studied _in vivo_ and _in vitro_ in rats given a 2- or 3-week dietary regimen of 2,4,5-TP (doses up to 800 mg/kg diet.) (Stroo et al., 1979). After dosing, renal excretion was evaluated in kidney slices or _in vivo_ by the elimination of p-aminohippurate (PAH). Although 2,4,5-TP competitively inhibited PAH secretion, the rapid recovery within 24 hours of the last dose of normal secretion indicates that chronic anion transport blockage did not occur. In a study on the renal handling of 2,4,5-T in dogs, Hook et al. (1976) demonstrated that the low clearance of 2,4,5-T was due to the fact that 2,4,5-T was more tightly bound to plasma protein (i.e., decreased amount of free 2,4,5-T was available for excretion).

Hiltibran (1975) found that 2,4,5-TP alters the oxygen and phosphate uptake by bluegill (_Lepomis macrochirus_) liver mitochondria in the presence of succinate or α-ketoglutarate as the mode of its toxic action. Oxygen uptake in this case was inhibited more than by 2,4,5-T or 2,4-D. However in absence of succinate or α-ketoglutarate 2,4,5-TP affected oxygen uptake less than 2,4,5-T.

Venkaiah and Patwardhan (1978) observed that 2,4,5-TP affected the rat liver mitochondrial energy transfer by inhibiting mitochondrial phosphorylation, and active ion uptake. 2,4,5-TP was also found to contract the swollen mitochondria by adenosine triphosphate.

Human Studies

To study the fate of silvex Sauerhoff et al (1977b) allowed one female and seven male healthy volunteers (weights: 56.7-94.8 kg) to ingest 1 mg/kg bw analytical grade free acid of silvex, [2-(2,4,5-trichlorophenoxy) propionic acid], of >99% purity, containing <0.01 ppm of 2,3,7,8-TCDD. Within 2-4 hours after ingestion the peak plasma levels were observed and the half-life for its clearance from plasma was found to be 4.0±1.9 and 16.5±7.3 hours for the initial and terminal phases, respectively. Within 24 hours after ingestion 65% of the administered dosage of silvex was excreted through urine as free silvex and silvex conjugate. No evidence of saturation kinetics could be observed by these authors at the administered dose level of 1 mg/kg. Its biphasic clearance from plasma and excretion through urine seem to be due to first-order kinetic.

Summary

Absorption of 2,4,5-TP and 2,4,5-T by the gastrointestinal tract of mammals following oral exposure is rapid and virtually complete, with >90% absorbed after doses of 0.04-200 mg/kg (Fang et al., 1973; Piper et al., 1973; Erne, 1966). Data on absorption after dermal or inhalation exposure to 2,4,5-TP and 2,4,5-T were not available. Following absorption, these compounds are rapidly distributed throughout the organism, although reversible binding to plasma protein results in a greater retention in the plasma compartment (Fang and Lindstrom, 1980; Senczuk and Pogorzelska, 1981). Highest tissue levels are in liver and kidney (Erne, 1966; Sauerhoff et al., 1977a).

2,4,5-TP and 2,4,5-T are not metabolized extensively since >93% of the administered oral doses were excreted unchanged in the urine of rats (Sauerhoff et al., 1976; Piper et al., 1973). Excretion of 2,4,5-T by rats was rapid ($t_{1/2}$ = 3.4 hours for adults; $t_{1/2}$ = 97 hours for neonates) (Fang et al., 1973). Urinary excretion of 2,4,5-TP and 2,4,5-T after high i.v. doses (50 and ≥100 mg/kg, respectively) to rats followed saturation kinetics, while a greater fraction was eliminated in feces, suggesting a greater role of biliary excretion at higher doses (Sauerhoff et al., 1977a).

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as 2,4,5-TP from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to 2,4,5-TP is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to 2,4,5-TP in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for 2,4,5-TP from drinking water, food and ambient air for the 70-kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources.

Exposure Estimation

Drinking Water. Levels of 2,4,5-TP in drinking water vary from one location to another. The highest level of 2,4,5-TP monitored in the available studies was >10 μg/ℓ (the current Maximum Contaminant Level) in North Carolina (FRDS, 1984). However, levels of 2,4,5-TP in drinking water typically appear to be somewhat lower. Analysis of the National Screening Program for Organics in Drinking Water (NSP) (Boland, 1981) suggests that median levels of 2,4,5-TP in drinking water systems would be <2.0 μg/ℓ, since none of 117 systems sampled contained a level of 2,4,5-TP >2.0 μg/ℓ. In addition, median levels of 2,4,5-TP are likely to be <0.1 μg/ℓ, since none of the 92 systems sampled in the Rural Water Survey (RWS) contained a level of 2,4,5-TP >0.1 μg/ℓ (U.S. EPA, 1984). 2,4,5-TP may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in exposure levels for 2,4,5-TP.

The daily intake of 2,4,5-TP from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that the daily intake of 2,4,5-TP from drinking water ranges from 0.0->0.29 μg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Diet. FDA reported that no significant dietary exposure to 2,4,5-TP is expected, based on the data in the FDA Total Diet Studies. Tolerances

TABLE IV-1

Estimated Intake of 2,4,5-TP from Drinking Water*

Drinking water concentration (μg/ℓ)	Intake (μg/kg/day)
0.0	0.0
0.1	0.0029
2.0	0.057
>10	>0.29

*Assumptions: 70-kg man consuming 2 ℓ of water/day.

set by U.S. EPA for 2,4,5-TP in and on raw agricultural commodities are 50 µg/kg for pears and 100 µg/kg in apples, plums, rice and sugarcane (FDA, 1981).

Air. No data were obtained on levels of 2,4,5-TP in ambient air. Therefore, the respiratory intake of 2,4,5-TP could not be estimated.

Summary

Data on the intake of 2,4,5-TP from drinking water, food and ambient air were insufficient for use in determining which of the three sources is the major contributor to total intake. U.S. EPA has reported a maximum safe level for 2,4,5-TP (from all sources) of 2 µg/kg/day (U.S. EPA, 1976).

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V. HEALTH EFFECTS IN ANIMALS

One of the major problems in assessing the effects of 2,4,5-TP is the contamination with varying amounts of 2,3,7,8-TCDD. Many investigators were unaware of the presence and amount of 2,3,7,8-TCDD in a sample and, therefore, this information has gone unreported in many studies. Consequently, whether the reported effects are attributable to 2,4,5-TP alone, the 2,3,7,8-TCDD contaminant, a combination of both, or additional contaminants such as the carrier or emulsifier is not clear in many studies.

The subsequent discussion will concern itself with the toxic effects of 2,4,5-TP and only consider 2,3,7,8-TCDD in its relationship to the phenoxy herbicides 2,4,5-TP and 2,4,5-T. Appropriate notations for 2,3,7,8-TCDD content have been included in the tables on acute, subchronic and chronic toxicity, and the "Contaminants" section presents limited quantitative data on the health effects of 2,3,7,8-TCDD.

Acute Effects

The single dose oral LD_{50}s for 2,4,5-TP range from ~600-1400 mg/kg bw for mice, rats, guinea pigs and rabbits for acid and ester formulations; for the acid, an LD_{50} of 650 mg/kg was determined in rats (Table V-1) (Rowe and Hymas, 1954). Gross general symptoms of intoxication include depression, posterior quarter muscle weakness, irritation of the stomach and minor liver and kidney damage. The mono-, di- and tripropylene glycol butyl ether esters are the least toxic formulations.

TABLE V-1

Acute Oral Toxicity of 2,4,5-TP (Acid, Ester, and Amine Formulations) in Experimental Animals[a]

Species/Strain	Formulation/Vehicle	Purity/TCDD Content	Sex/No.	Dose (mg/kg bw) (19/20 confidence limits)	Effects
Mice/NR	PGBE esters[b] (mono-, di-, tri)/corn oil	NR/NR	F/NR	1410 (1000-2000)	LD_{50}
Rats/NR	acid/corn oil	NR/NR	M-F/NR	650 (560-760)	LD_{50}
Rats/NR	mixed butyl esters/ corn oil	NR/NR	F/NR	600 (250-1000)	LD_{50}
Rats/NR	PGBE esters (mono-, di-, tri-)/corn oil	NR/NR	F/NR	621 (473-814)	LD_{50}
Guinea pigs/NR	PGBE esters (mono-, di-, tri-)/corn oil	NR/NR	M/NR	1250 (range: 500-2000)	LD_{50}
Rabbits/NR	mixed butyl esters/ undiluted	NR/NR	F/NR	750 (500-1000)	LD_{50}
Rabbits/NR	PGBE esters (mono-, di-, tri-)/undiluted	NR/NR	F/NR	819 (610-1070)	LD_{50}

[a] Source: Rowe and Hymas, 1954

[b] PGBE = propylene glycol butyl ether

NR = Not reported

Subchronic Exposure

Data on the subchronic toxicity of 2,4,5-TP in experimental animals are scarce. There are, however, data from two unpublished Dow Chemical Company reports available in a review document on phenoxy herbicides (NRCC, 1978). The data from these studies are summarized in Table V-2. Oral administraton of 5 mg/kg bw/day of 2,4,5-TP to rats for 90 days in the diet produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas a dose of 2 mg/kg bw/day was reported to be a NOEL in dogs (parameters measured were not reported in NRCC, 1978) (Dow Chemical Company, 1963).

Chronic Exposure

The only information available on the chronic toxicity of 2,4,5-TP (other than from an oncogenic study) comes from unpublished investigations using rats and dogs (Dow Chemical Company, 1962). A 2-year dietary regimen of a potassium salt of 2,4,5-TP (0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day) only revealed a significant increase in relative kidney:body weight ratios in rats of both sexes at doses >0.26 mg a.e./kg bw/day (Dow Chemical Company, 1962; Gehring and Betso, 1978). Other parameters measured in this study were body weight, survival, food intake, clinical chemistry, hematology, tumor incidence and gross or histopathology. No effects were seen in these parameters except for a decrease in body weight in male rats at the highest dose. Because of the absence of morphological alterations in the kidney at any dose level, these investigators felt that the increase in kidney weight reflected a physiological adaptation rather than an adverse effect (Table V-3) (Dow Chemical Company, 1962; Gehring and Betso, 1978). Mullison (1966) reviewed this beagle dog study of the Dow Chemical Company.

TABLE V-2

Subchronic Oral Toxicity of 2,4,5-TP Formulations in Experimental Animals*

Species/ Strain	Formulation/ Vehicle	Purity/TCDD Content	Sex/No.	Age/wt.	Dose (mg/kg bw/day)	Duration	Effects
Rats/NR	sodium salt or PGBE ester/diet	NR/NR	M-F/NR	NR/NR	5 mg a.e.	90 days	increase in relative weight of liver and kidney with "histopathologic changes" in both
Dogs/NR	NR/diet	NR/NR	NR/NR	NR/NR	2 mg a.e.	89 days	"no-effect level"

*Source: Dow Chemical Co., 1962, 1963

PGBE = propylene glycol butyl ether; a.e. = acid equivalent; NR = Not reported

TABLE V-3

Chronic Oral Toxicity of 2,4,5-TP Formulations in Experimental Animals

Species/Strain	Formulation/Vehicle	Purity/TCDD	Sex/No.	Age/wt.	Dose/Duration	Effect
Rats/Wistar	potassium salt/diet	NR/NR	M-F/30+30	NR/NR	0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day x 2 years (some animals were sacrificed at 12 and 18 months)	No effect on survival, food intake, clinical chemistry, hematology, tumor incidence, gross pathology or histopathology; there was noted an increase in relative kidney weight at all doses in males and a decrease in body weight in males at the highest dose (statistical significances not specified)
Dogs/Beagle	potassium salt/diet	NR/NR	M-F/4+4	NR/NR	0.9 mg a.e./kg bw/day x 2 years	No effect on body weight, food intake, hematology, blood urea nitrogen, alkaline phosphatase, bromsulfophthalein dye retention, organ weights, or histopathology
					2.6 mg a.e./kg bw/day x 2 years	Mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in males
					8.2, 9.9 mg a.e./kg bw/day x 2 years (in (M and F, respectively)	Same liver changes as described for intermediate dose in both males and females plus elevated levels of SGPT and SGOT in females

*Source: Gehring and Betso, 1978

a.e. = acid equivalents; NR = Not reported

The dogs fed 0.9 mg a.e./kg bw/day (actual dose 0.75 mg/kg/day) for 2 years, had no effects on body weight, food intake, hematology, blood urea nitrogen or histopathology (Mullison, 1966). Evidence of adverse effects on the livers of male dogs, however, was observed at 2.6 mg a.e./kg bw/day 2,4,5-TP. Both male and female dogs were affected at doses of 8.2 and 9.9 mg a.e./kg bw/day, respectively (Gehring and Betso, 1978). This 2-year feeding study of 2,4,5-TP resulted in mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in males at 2.6 mg a.e/kg bw/day dosage. Similar liver changes observed at 2.6 mg a.e/kg bw/day, accompanied by elevations of SGOT and SGPT levels (elevations were not specified by the author) were observed at 8.2 (male) and 9.9 mg a.e./kg bw/day (female) dosages in this study. A NOAEL was judged to be 0.9 mg a.e./kg bw/day.

Synergistic and Antagonistic Effects

The nature of the interaction between 2,4,5-TP and 2,3,7,8-TCDD is not well understood. In many studies, it is not clear whether the reported effects are due to 2,4,5-TP alone, the 2,3,7,8-TCDD contaminant or a combination of both. Further data regarding the interaction between 2,4,5-TP and 2,3,7,8-TCDD could not be located in the available literature.

Carcinogenicity

Innes et al. (1969) reported that tumor incidences were not significantly increased at any site in B6C3F1 or B6AKF1 mice (18/sex/strain) that were treated daily by gavage from 7-28 days of age with 46.4 mg/kg bw/day of 2,4,5-TP in 0.5% gelatin, and subsequently maintained for 76-77 weeks on a diet that contained 121 ppm 2,4,5-TP. The doses administered were the maximum tolerated that had been selected from prechronic studies. If it is assumed that mice consume 13% of their weight in feed each day, the estimated daily TWA dose of 2,4,5-TP was 17.2 mg/kg/day. By current standards there are a number of deficiencies in this study, which makes it inadequate for assessing the carcinogenic potential (only one dose level, too few animals, only 18 months of exposure). Statistically significant incidences of tumors were also not observed at specific sites in the same strains of mice (18/sex/strain) 18 months after single s.c. injections of 215 mg/kg 2,4,5-TP (in DMSO) on day 28 of age. Complete necropsies that included gross and histological examination of major organs and tissues were performed on all treated and control animals. As with the oral study, the study has deficiencies that render it inadequate to serve as a sensitive assay for carcinogenic activity. Male B6C3F1 mice that were treated orally or by s.c. injection did show a higher incidence of total tumors (8/17 and 7/18 in treated vs. 22/79 and 2/24 in controls, respectively), but this was not apparent in female B6C3F1 or B6AKF1 mice of either sex.

Groups of Wistar rats (30 males and 30 females in each group) were fed diets containing 0.0, 0.03, 0.003 and 0.001% Kurosol®SL (potassium salt of silvex) for up to 24 months (Gehring and Betso, 1978). Administration of the test compound began at 50 days of age. Animals were sacrificed at 12 and 18 months so that the group sizes at the end of the 2-year study could not have been more than 21 or 22 per sex; they may have been even smaller. However, the size of the groups at the end of the study cannot be exactly determined since no data were provided on the extent to which animals, other than the ones sacrificed, died before the end of the study.

There was no evidence of a toxic effect or reduced survival in female rats administered any dose compared with controls. Therefore, it does not appear that the females were administered the maximum tolerated dose. Since high-dose males exhibited a significant decrease in average body weights, it appears that they were administered a maximum tolerated dose.

No significant increase in tumors was reported. However, because small groups of animals were used and the maximum tolerated dose was apparently not used in the high-dose females, this study cannot be considered as significant evidence of the noncarcinogenicity of silvex in rats.

Groups of beagle dogs (four males and four females in each group) were fed diets containing 0.0, 0.056, 0.019 and 0.0056% Kurosal®SL (potassium salt of silvex) (Gehring and Betso, 1978). One male and one female of each group were killed at 12 months. The remaining animals were killed at the end of the 2-year period.

No incidence of tumors was observed. However, this study does not constitute a valid cancer study because its duration was far less than the life expectancy of a beagle dog and the sizes of the animal groups were exceedingly small. Therefore, this study provides no evidence of the lack of carcinogenicity of silvex in dogs (Gehring and Betso, 1978).

Current data indicate that 2,3,7,8-TCDD, a known contaminant of 2,4,5-TP, 2,4,5-trichlorophenoxyacetic acid and 2,4,5-trichlorophenol are carcinogenic in rats maintained on 2,3,7,8-TCDD supplemented diets for 2 years (Kociba et al., 1978). Rats fed 0.01 μg/kg bw/day 2,3,7,8-TCDD demonstrated an increased incidence of liver lesions (including hepatocellular nodules) and lung lesions (including focal alveolar hyperplasia). Ingestion of 0.1 μg/kg bw/day caused an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates or tongue, compared with controls. Mice show increased incidence of hepatocellular carcinomas, thyroid tumors, subcutaneous fibrosarcomas and histiocytic lymphomas (U.S. EPA, 1985). The U.S. EPA (1985) has given 2,3,7,8-TCDD a Group B2 weight of evidence ranking meaning that 2,3,7,8-TCDD is carcinogenic in animal test systems and should be considered to be a probable carcinogen for humans.

Mutagenicity

The mutagenicity of 2,4,5-TP was evaluated in a single study. In an Ames assay performed on over 100 herbicides for their possible mutagenicity, Anderson et al. (1972) found that 2,4,5-TP failed to revert eight Salmonella typhimurium strains to histidine independence. The strains were not specified, but were designated as nonsense (amber or ochre), missense or frameshift mutants (the mutations involved the C, D and G gene of the histidine operon). The plate incorporation technique was used, but a metabolic activation system was not employed. Approximately 1-5 μℓ of the surveyed chemicals were applied per plate, but the specific concentration of 2,4,5-TP tested was not stated.

Teratogenicity and Other Reproductive Effects

Only two studies have been encountered on the potential teratogenic activity of 2,4,5-TP. Courtney (1977) administered 2,4,5-TP to pregnant CD-1 mice at a dose level of 1.5 mM/kg/day (~398 mg/kg/day) on days 12 through 15 of gestation. The compound was administered both by gavage using corn oil:acetone (9:1) as the vehicle and by s.c. injection using DMSO as the vehicle. Administration through both routes caused a significant ($p<0.01$) increase in maternal weight (probably caused by increased liver weight) and a significant ($p<0.001$) increase in maternal liver-to-body weight ratios. Oral and s.c. exposures to 2,4,5-TP were associated with decrease in fetal weight and increased incidences (7 and 3%, respectively) of cleft palate. The prenatal developmental indices were determined by the author to be 88 and 66 for oral and s.c. exposures, respectively.

The other study on the teratogenicity of 2,4,5-TP is an unpublished study by Dow Chemical Company, summarized in U.S. EPA (1979a). Because the summary is so brief it is reproduced in full below:

> Dow Chemical Company studied the reproductive effects of silvex and the propylene glycol butyl ether ester of silvex (silvex-PGBE), each containing <0.05 ppm TCDD. Sprague-Dawley rats were exposed to 25-100 mg/kg of silvex on days 6-15 of gestation. Significant effects on fetal mortality and birth weight were observed in the litters of treated dams. Skeletal anomalies, such as cleft palate, retarded ossification and extra cervical ribs were observed among the exposed fetuses. Micropthalmia (abnormal smallness of the eye-ball) and cardiovascular abnormalities were also seen. Similar effects were observed when animals were dosed with silvex-PGBE, or when dosed for three-day intervals during the period of early organogenesis.

Micropthalmia represents abnormal smallness of the eye, not eyeball as stated above.

Contaminants

Early studies using 2,4,5-TP must be cautiously interpreted because the herbicide samples may have been contaminated with a high concentration of

2,3,7,8-TCDD. In the early 1960s the TCDD content in commercial 2,4,5-T and 2,4,5-trichlorophenol ranged from 5-50 ppm. By the early 1970s the manufacturers had set a limit of 0.1 ppm TCDD contamination. Since 2,4,5-TP is derived from 2,4,5-trichlorophenol, the same TCDD contamination levels would be assumed to occur in 2,4,5-TP. Reported effect/no-effect levels would be expected to be conservative; however, a high content of 2,3,7,8-TCDD would suggest greater toxicity than would be the case if purer herbicide samples had been used. The 2,3,7,8-TCDD contaminant is highly toxic, with symptoms appearing at chronic doses as low as 0.01 μg/kg bw/day in rats (Kociba et al., 1978). In this study a NOEL was reported at 0.001 mg/kg/day (22 ppt in the diet). The single oral LD_{50} for 2,3,7,8-TCDD ranges from 0.6 μg/kg in male guinea pigs to 115 μg/kg in rabbits (Schwetz et al., 1973). Mortality from acute oral poisoning is usually delayed, preceded by symptoms such as dehydration, alopecia and inactivity.

Summary

The acute oral LD_{50} for 2,4,5-TP in rats is 650 mg/kg (Rowe and Hymas, 1954). Subchronic exposure of 2,4,5-TP in rats (5 mg/kg/day for 90 days) produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas 2 mg/kg/day for 89 days was reported to be a NOEL in dogs (Dow Chemical Company, 1963). Adverse effects such as mild degeneration and necrosis of hepatocytes accompanied by elevations of SGOT and SGPT were observed in dogs fed 2.6, 8.2 and 9.9 mg/kg/day for 2 years (Gehring and Betso, 1978). A NOEL was judged to be 0.9 mg a.e./kg bw/day in dogs in this chronic study. A 2-year dietary regimen of 2,4,5-TP revealed an increase in relative kidney:bw ratio in rats at doses >2.6 mg/kg/day (Gehring and Betso, 1978).

The nature of the interaction between 2,4,5-TP and 2,3,7,8-TCDD is not understood and pertinent data regarding this interaction could not be located in the available literature.

Only limited data concerning the potential carcinogenicity of 2,4,5-TP are available. Chronic oral exposure to 2,4,5-TP did not elicit significantly increased incidences of tumors at any site in two strains of mice exposed to ~17.2 mg/kg/day for 80-81 weeks (Innes et al., 1969), in rats exposed to 7.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978) or in dogs exposed to 9.9 mg a.e./kg/day for 2 years (Gehring and Betso, 1978). None of these studies qualify, however, as adequate animal bioassays for reasons of less than lifetime exposure or too few exposed animals. Based upon the available (albeit inadequate) bioassay data, the weight of evidence for 2,4,5-TP is equivalent to Group D, meaning in this case that the few available studies are inadequate to assess the human carcinogenic potential. However, the likely presence of a 2,3,7,8-TCDD contaminant in the commercial 2,4,5-TP products gives rise to a public health concern regarding exposure to 2,4,5-TP. Depending upon when the 2,4,5-TP was manufactured, the range of TCDD contaminant could range from 0.1 ppm from early 1970 to as much as 5-50 ppm in the 1960s. There is reason to consider 2,4,5-TP as having the same human carcinogenic potential as 2,3,7,8-TCDD, which is EPA Group B2, if the 2,4,5-TP product is thought or verified to have a hazardous level of TCDD as a contaminant.

Only two studies have been located on the potential teratogenic activity of 2,4,5-TP (Courtney, 1977; U.S. EPA, 1979a). Both studies reported teratogenic effects at dose levels of -398 mg/kg/day and 25-100 mg/kg/day in mice and rats, respectively; however, the lack of conclusive evidence from these studies precludes the evaluation of the teratogenic potential of 2,4,5-TP. Doses of 25-100 mg Silvex-PGBE/kg bw contaminated with <0.05 ppm TCDD did cause definite teratogenic effects in rats (U.S. EPA, 1979a).

VI. HEALTH EFFECTS IN HUMANS

Introduction

Observations in Humans. A primary risk to human health could arise from occuptional exposure during the manufacture and use of 2,4,5-T and 2,4,5-TP. The available occupational studies, however, have assessed the effects of mixed exposures of chlorophenoxy herbicides (including 2,4,5-T), chlorophenols and other compounds.

Acute Exposure

Pertinent data regarding the effects resulting from acute exposure of 2,4,5-TP to humans could not be located in the available literature.

Subchronic and Chronic Exposure

In a study of 56 workers who were employed in the manufacture of 2,4,5-T and 2,4-D, Singer et al. (1982) reported a significant correlation ($p<0.004$) between duration of employment and reduction of nerve conduction velocities of sural nerves. Conduction velocities of the sural nerves of the phenoxy herbicide-exposed workers (average exposure = 7 years) was 40.3 m/second, while values for a control group of 25 nonexposed workers was 42.8 m/second ($p=0.02$). Singer et al. (1982) noted that these electrophysiologic responses may be due to the 2,4-D or 2,3,7,8-TCDD contaminants, and not to 2,4,5-T alone.

Case Reports and Epidemiologic Studies on Carcinogenicity. Observations of an unusual occurrence of relatively rare soft-tissue sarcomas in populations exposed to phenoxyherbicides were first made by Hardell (1977).

Of some 87 patients seen from 1970-1976 at the Department of Oncology, University Hospital, Umea, Sweden, seven individuals with soft-tissue sarcomas were identified. All seven had been occupationally exposed to phenoxy acids 10-20 years earlier. The tumors were 2 leiomyosarcomas, 1 liposarcoma, 1 rhabdomyosarcoma, 1 myxofibrosarcoma and 2 additional sarcomas of which the histopathology was uncertain, but one was probably a neurofibrosarcoma and the other a rhabdomyosarcoma. The clustering of this rare tumor type among these patients prompted the author to suggest that epidemiological studies be done to determine if exposure to phenoxy acids and the impurities they contain are related to the occurrence of soft-tissue sarcomas.

Zack and Suskind (1980) reported a soft-tissue sarcoma death in a cohort study of workers exposed to 2,3,7,8-TCDD in a trichlorophenol process accident in Nitro, West Virginia. This tumor, a fibrous histiocytoma, was noted by the author as a rare event. This study, referred to as the Nitro study, is discussed later.

In a cohort mortality study where 61 male employees in a trichlorophenol manufacturing area had exhibited chloracne following a 1964 exposure incident, four deaths were noted by the end of his study period, one of which was due to a fibrosarcoma (Cook et al., 1980). The authors did not seem to attribute any special significance to this finding at the time.

In a cohort mortality study, 204 employees were exposed to 2,4,5-T during its manufacture from 1950 to 1971; no soft-tissue sarcomas were found among 11 deaths that had occurred by 1976 (Ott et al., 1980). One of these 11 deaths was due to a malignant neoplasm.

In a review of the studies of Zack and Suskind (1980), Cook et al. (1980), an unpublished study by Zack (in which a liposarcoma was found), a study by Ott et al. (1980) and Honchar and Halperin (1981) noted 3 (2.9%) soft-tissue sarcomas in a total of 105 deaths. Among U.S. males aged 20-84, 0.07% of the deaths were reported as soft tissue sarcomas (ICD 171, 8th Revision, 1975)* indicating an unusual excess of such tumors. This may be an underestimate because of the possibilities that some soft-tissue sarcomas may have been coded to categories other than ICD 171. Individually, none of the reported case studies reported a significant excess of soft-tissue sarcomas.

Cook (1981) found an additional malignant fibrous histiocytoma after a later review of the medical records from his earlier cohort study. Cook (1981), who was familiar with the three earlier cases, noted that frank chloracne occurred previously in two cases of the four having a diagnosis of malignant fibrous histiocytoma. A third person diagnosed as having a fibrosarcoma worked in a trichlorophenol (TCP) process area contaminated with 2,3,7,8-TCDD. This individual exhibited facial dermatitis but there was no diagnosis of chloracne. The fourth case (diagnosed as a liposarcoma) was an individual who had been employed earlier in a plant producing 2,4,5-T. Cook et al. (1980) noted that although chloracne was not reported, it could not be discounted. The authors also noted that all four were cigarette smokers and suggested that smokers with chloracne caused by 2,3,7,8-TCDD exposure may be subject to an increased risk of fibrous soft-tissue sarcomas, although no prior reports have shown soft tissue sarcomas associated with cigarette smoking.

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*Department of Health, Education, and Welfare. U.S. Public Health Service. National Center for Health Statistics of the United States, 1974. Vol. II. Mortality, Part A.

Hardell and Eriksson (1981) discounted this hypothesis by citing that only one of the seven cases exhibited chloracne before the appearance of the soft-tissue saromcas, and that in a subsequent later case control study, no difference was found in smoking habits between the cases noted and controls.

Moses and Selikoff (1981) reported a fifth soft-tissue sarcoma in a worker employed at the Monsanto Chemical Company at a time when trichlorophenol and 2,4,5-T were being produced. The worker died of a retroperitoneal neurogenic sarcoma (malignant schwanoma) in 1980 at the age of 58. The employee, before his death, in a detailed occupational history said that he believed he was exposed to these chemicals while he was a truck driver, hauler and maintenance worker, but that he did not work in the production of either chemical. He was a nonsmoker and had no history of chloracne.

Johnson et al. (1981) treated a father and son with soft-tissue sarcomas (the 33-year-old son was diagnosed as having a fibrosarcomatous mesothelioma, while the 53-year-old father had a liposarcoma). Both were exposed to halogenated phenol derivatives. The authors noted that 2,4-dichlorophenol can be a precursor of 2,4-D and 2,4,5-T. The father had experienced prolonged exposure before his disease. The son supposedly had a shorter latency, according to the author. In neither case was the follow-up time given.

Sarma and Jacops (1981) reported three cases of thoracic soft-tissue sarcoma in individuals who were presumably exposed to Agent Orange while serving in Vietnam. The diagnoses were fibrous histiocytoma, mediastinal fibrosarcoma, and a pleural/diaphragmatic leiomyosarcoma. All three served in areas where defoliants were used at the time. One was drenched with the material in one spraying.

Bishop and Jones (1981) found two cases of non-Hodgkin's lymphomas of the scalp in a related clinical study of 158 employees of a pentachlorophenol manufacturing plant in Wales. Homologues of 2,3,7,8-TCDD occurred as contaminants at up to 300 ppm at intermediate manufacturing stages and 5 ppm in the final products. Mild, moderate and severe cases of chloracne were seen in many employees, including the two men who subsequently developed lymphomas. Both men worked in processes where exposure to other chemicals occurred, including exposure to aromatic hydrocarbons. The authors reported that only 0.28 tumors of this type could be expected to occur in a group of 158 workers (ICD 200 and 202), although the basis for the computation of expected numbers is not stated.

Olsson and Brandt (1981) noted that of 123 male patients seen at their clinic in Sweden with a recent diagnosis of non-Hodgkin's lymphoma (NHL), 5 had cutaneous lesions as the only clinically detectable manifestation of

NHL. Four of the five were reported to have repeatedly sprayed large areas with phenoxy acid herbicides. In the remaining 118 NHL patients, only seven had a similar occupational exposure to phenoxy acids. The authors reported this to be significant at $p<0.001$. Olsson and Brandt (1981) suggested that a relationship exists between cutaneous presentation of NHL and occupational exposure to phenoxy acids, and believed their observations were similar to those of Bishop and Jones (1981).

The total number of workers with these illnesses who were exposed to phenoxy acids and/or chlorophenols is small, but considering the rarity of this cancer, it is unusual that so many cases of soft-tissue sarcomas have occurred. A Lancet editorial (Anonymous, 1982) calls this phenomenon "disturbing."

Soft-tissue Sarcomas -- Soft-tissue sarcomas (STS) constitute a collection of heterologous lesions that include both malignant and nonmalignant tumors. Not all of them have their origin in primordial mesenchymal cells. Some exceptions are tumors of peripheral nerves, and neuroectodermal tumors that are classified as STS but are derived from nonmesenchymal cells. Classification, grading and staging of STSs is difficult because of the capacity of such cells to differentiate into many different tissues. Fairly precise histogenetic classification of such tumors is accomplished through consideration of growth patterns and cell morphology and evaluation of intracellular and extracellular products of tumor cells. There are a dozen distinctly different classes of mesenchymal cells that develop into the following six well-defined tissue complexes: fibrous tissue, tendosynovial tissue, adipose tissue, muscle, vessels and bone. STSs can be induced in any of these tissue types (Hajdu, 1983). The classification of STSs for cause of death coding in the ninth and latest revision of the International Classification of Diseases (ICD, 1975) places STSs into one of several categories. But chiefly, they fall into "malignant neoplasms of connective and other soft-tissue" (ICD 171). Lymphosarcomas, retroperitoneal sarcomas and extra skeletal STSs of the bone are coded elsewhere. In some instances, if site is mentioned, it is coded to the site [i.e., leiomyosarcoma of the stomach (ICD 151.9), neurofibroma of the chest wall (215.4)].

Questions have been raised concerning the appropriateness of lumping together malignant tumors of different sites and tumor types in order to derive risk estimates. It may not be scientifically appropriate to do so because an elevated risk cannot readily be ascribed to a particular site or type as is usual with most carcinogenic chemicals and substances. Unfortunately, with respect to STSs, tallies of deaths from STSs of particular sites and types are not maintained separately by the vital statistics offices because of their rarity; therefore, it is impossible to derive risk estimates for particular types at given sites. Altogether, ~2000 deaths/year can be attributed to STSs in the United States, most of which are coded to ICD category 171 for purposes of developing incidence and mortality rates for this composite cause. Within ICD 171, individual types that may be correlated with exposure cannot be identified.

A separate problem that potentially could arise from assigning STSs to multiple ICD codes is that incidence and death rates from STSs may be underestimated. Furthermore, risk estimates derived from dividing observed cases (or deaths) by expected cases (or deaths) could be biased upward. This could happen when observed STSs classified to ICD codes other than ICD 171 are lumped together in ICD 171 while expected STSs are based upon STSs classifiable to ICD 171 only. Thus, action of this sort, especially with respect to cohort studies of individuals exposed to dioxin-containing herbicides and/or chlorophenols, could lead to risk estimates that may be biased upward by the inclusion of STSs in the observed category for risk estimation that should be coded to categories other than 171.

Prompted by clinical observations over a 7-year period of malignant sarcomas in seven men with previous occupational exposure to phenoxyacetic acid herbicides (Hardell, 1977), researchers at the Department of Oncology, University Hospital, Umea, Sweden, initiated case-control epidemiologic studies to test the hypothesis of an etiologic association (Hardell and Sandstrom, 1979). Cases were defined as male patients with sarcomas of soft connective tissue, such as smooth muscle (leiomyosarcoma) and fat (liposarcoma). The distribution of tumor types in the two studies is shown in Table VI-1. Sarcomas of tissues, such as bone and cartilage, were excluded as cases. According to the authors, these tumors may have a different etiology and there occurred a different age-distribution in patients with these tumors as compared with that of STS (Hardell, 1983).

TABLE VI-1

Distribution of Tumor Types in Two Case-Controls Studies of Soft-Tissue Sarcoma

Diagnosis	Tissue of Origin	Percent of Cases	
		Study A[a] (n=52)	Study B[b] (n=110)
Leiomyosarcoma	Smooth muscle	30	23
Fibrous histiocytoma	Subcutaneous connective tissue	17	25
Liposarcoma	Fat tissue	14	6
Neurogenic sarcoma	Nerve tissue	10	4
Angiosarcoma	Blood vessels	8	2
Myxosarcoma	Primitive connective tissue	6	8
Fibrosarcoma	Fibrous tissue	4	8
Other sarcomas		11	24
Total		100	100

[a] Unpublished information supplied by Hardell to EPA (Hardell and Sandstrom, 1979)

[b] Eriksson et al., 1979, 1981

Two case-control studies were conducted: the first in northern Sweden (referred to below as Study A) and the second in the southern part of the country (Study B). The exposures to the substances of primary interest are shown in Table VI-2. In the north (Study A), occupational exposure to phenoxyacetic acids took place in both forestry and agricultural work. In the south (Study B), these exposures were predominantly agricultural. The phenoxyacetic acids to which exposure occurred consisted predominantly of 2,4,5-T and 2,4-D in both studies. Exposure to 2,4,5-T in the absence of 2,4-D was rarely reported in either study. Exposure to chlorophenols, which contain chlorinated dibenzodioxin impurities (Levin et al., 1976), occurred mostly in sawmill work and paper pulp production. Very few persons reported exposure both to phenoxyacetic acid and chlorophenols in these studies. Of the two predominant phenoxyacetic acids, only 2,4,5-T is known to be contaminated with 2,3,7,8-TCDD. In Study B, a relative risk of 4.9 (90% confidence intervals 1.6-11.1) was found in relation to exposure to phenoxyacetic acid herbicides other than 2,4,5-T (2,4-D, MCPA, mecoprop, dichloroprop).

Relative risks in relation to the three major categories of exposure are shown in Table VI-3.* Studies A and B indicate a risk of developing STSs among workers exposed to phenoxyacetic acids only, chlorophenols only, or phenoxyacetic acids and/or chlorophenols several times higher than among persons not exposed to these chemicals. In each comparison, the relative risk is high and was thus unlikely to have resulted by chance alone.

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*In the analyses considering phenoxyacetic acids only and chlorophenols only, persons exposed to the other categories of substances were excluded. In Study A, the three persons exposed to both chlorophenols and phenoxyacetic acids were included in all comparisons.

TABLE VI-2

Exposure Frequencies in Two Case-Control Studies of Soft-Tissue Sarcoma

Substance(s)	Percent Exposed			
	Study A		Study B	
	Cases (n=52)	Controls (n=206)	Cases (n=110)	Controls (n=219)
Phenoxyacetic acids only	23.1	6.3	12.7	2.3
Chlorophenols only	11.5	2.4	10.0	3.6
Both	1.9	0.5	0	0
Total	36.5	9.2	22.7	5.9

*Sources: Study A, Hardell and Sandstrom, 1979; Study B, Eriksson et al., 1979, 1981

TABLE VI-3

Relative Risks of Soft-Tissue Sarcoma in Relation to Exposure to Phenoxyacetic Acids and Chlorophenols in Two Case-Control Studies[a]

	Phenoxyacetic Acids Only		Chlorophenols Only		Phenoxyacetic Acids and/or Chlorophenols	
	Study A	Study B	Study A	Study B	Study A	Study B
Relative risk[b]	5.3	6.8	6.6	3.3	5.7	4.7
90% Confidence interval[c]	2.7-10.2	3.1-14.9	2.8-15.6	1.6-7.0	3.2-10.2	2.7-8.3
Significance level[d]	<0.001	<0.001	<0.001	<0.005	<0.001	<0.001

[a] Source: Study A, Hardell and Sandstrom, 1979; Study B, Eriksson et al., 1979, 1981

[b] Unmatched odds ratio

[c] Test-based method of Miettinen, 1976

[d] Chi square statistic, no continuity correction, one-tailed test

Since little is known of the etiology of STSs, the consideration of confounding in these studies was largely a hypothetical matter. The authors presented the effects of age, sex, and place of residence as possible confounding factors in the selection of controls.* Because of the high correlation between exposure to the substances of interest and employment in agriculture and forestry, a possible alternative hypothesis could be that some other unknown factor present in these occupations was responsible for the elevated relative risks.

To test this hypothesis, it is possible to calculate the relative risk in relation to the phenoxyacetic acid exposure in Study B, restricting the analysis to workers within agriculture and forestry. The result is a relative risk of 6.1 (90% confidence interval 2.4-15.4). This finding suggests that a confounding risk factor for STS distributed throughout agriculture and forestry work was not responsible for the overall increase in risk found in relation to phenoxyacetic acid exposure.

Because exposure histories were obtained by means of questionnaires and interviews, the major potential source of bias in these studies stems from the need to rely upon the personal recollection of cases and controls for exposure histories. The published papers indicate that the researchers paid a great deal of attention to this potential problem and specific efforts were made to avoid it during the conduct of the study.

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*Controls were matched individually to cases on the basis of these factors. Unmatched analyses are presented in Table VI-2 for the sake of simplicity. The matched-method relative risks for exposure to phenoxyacetic acids and/or chlorophenols were 6.2 ($p<0.001$) in Study A and 5.1 ($p<0.001$) in Study B.

In addition, the relative risk calculated by considering the agriculture and forestry workers who did not report exposure to phenoxyacetic acids or chlorophenols and comparing them with unexposed persons in other occupations was 0.9 (90% confidence interval 0.3-2.4) in Study B. This suggests that little recall bias was present (Axelson, 1980).

In an update of their earlier study, Eriksson et al. (1981) obtained information on the effects of phenoxy acids in the absence of the impurities -- polychlorinated dibenzodioxins and dibenzofurans. The risk ratio given exposure to phenoxy acids free of polychlorinated dibenzodioxins and dibenzofurans equaled 4.2 based upon 7 of 14 respondents who indicated exposure to phenoxy acid herbicides. When consideration was given to persons exposed only to phenoxy acids that contain such impurities, the relative risk was 17.0. A description of the basis for the determination of exposure or nonexposure to dioxins was not well presented in this study.

The author concluded that exposure to phenoxy acids and chlorophenols "might constitute a risk factor in the development of soft-tissue sarcomas." This risk relates not only to 2,4,5-trichlorophenoxy acids containing dioxin impurities but to other phenoxy acids as well. Some doubt was raised concerning the possible misclassification of individuals who were exposed to phenoxy acids free of polychlorinated dibenzodioxins [i.e., in particular, "dichloroprop" in the Eriksson et al. (1981) study]. In a recent communication from Hardell (1983), Eriksson recalculated his risk estimates after reclassifying his dichloroprop-exposed cases and controls into the category of probable exposure to phenoxy acids contaminated with polychlorinated dibenzodioxins and removing them from the nonexposed category. His new estimates were 4.0 based upon 5 of 8 respondents who were exposed to phenoxy acids allegedly free of contamination and 10.9 for those exposed to contaminated phenoxy acid. The first estimate was of only borderline significance utilizing the Mietinen test based statistic, thus, weakening any finding that the risk of STS extends to phenoxy acids free of dioxin.

In a cohort mortality investigation, Cook et al. (1980) studied 61 males involved in a 1964 exposure incident who had absorbed 2,3,7,8-TCDD through the skin and developed chloracne. The skin lesions characterizing chloracne ranged from a few comedones on the back of one employee (predating his entry into the process area where exposure could occur) to severe cysts and comedones over the faces, scalps, ears, necks and backs of the remaining employees of the group. Since the main route of exposure was not through the respiratory tract, no measurements of dioxin in the air were provided by the author. On the other hand, the author divided the cohort of 61 males into potentially "high" vs. "low" exposure by place of work based upon dermal exposure, although not stated. Vital status was traced from the data of the incident through 1978. Altogether only 4 deaths were observed by the end of the follow-up, vs. 7.8 expected. Of these, 3 were cancer deaths vs. 1.6 expected. The remaining death was hypersensitive heart disease vs. 3.8 expected. The histopathologic causes of death of the three cancer victims were 1) fibrosarcoma, 2) glioma with metastases, and 3) adenocarcinoma. The authors reported that all three victims smoked a minimum of one pack of cigarettes a day for "many years." Not enough information is provided by the authors to conclude that any of these four deaths were related to smoking. Site of tumor is not mentioned in the cancer deaths.

Cancer mortality is slightly elevated in this cohort. The study has low sensitivity and lacks a sufficient latent period. This increased mortality was not attributable to any particular cause and no deaths were attributable to liver cancer. Additionally, the authors stated that only one of the cancer deaths possessed "documented" evidence of chloracne, although this appears to be at variance with the definition of the cohort, which was reported by the authors to consist of males who reported to the medical department with skin conditions subsequently "diagnosed as chloracne." The authors concluded that the latency period was sufficient to "allow the identification of a potent human carcinogen," since it "exceeded 14 years." Orris (1981) noted that in the Hardell and Sandstrom (1979) study the authors stated that the latent period for soft-tissue tumors may be as long as 27 years and for many, over 14 years. In any case, Hueper and Conway (1964) noted that the latent period for the chemical induction of solid malignant tumors in man exceeds 15 years and is probably <30 years.

Smith et al. (1982b) conducted an initial case-control study of 102 males identified from the New Zealand Cancer Registry as having STSs (ICD 171) between 1976 and 1980. For each case, three controls each with another form of cancer were matched by age and year of registration. The selection of cancer controls from the same registry was done to eliminate recall bias and/or interviewer bias. The distribution of histological types in the cases is given in Table VI-4. An interview to elicit occupational history information was accomplished by telephone either with the next of kin to the patient or the patient himself if he was well enough, although the information was not used in this preliminary analysis.

TABLE VI-4

Distribution of Histological Types of Soft-Tissue Sarcomas*

Cell Type	Number of Cases	Percent
Fibrosarcoma	25	24
Liposarcoma	20	20
Rhabdomyosarcoma	9	9
Leiomyosarcoma	7	7
Malignant Histiocytoma	6	6
Other	22	21
Unspecified	13	13
Total	102	100

*Source: Smith et al., 1982b

Comparisons between cases and controls were accomplished by use of occupational groupings according to the Standard Classification System of New Zealand focusing on those occupational groups with a potential for exposure to phenoxy herbicides and chlorophenols. Expected cases for each major occupational classification were derived based upon the occupational distribution of the controls. The authors found no unusual excess of cases of STS in any major occupational category. In agriculture, forestry and fishing, 14 cases were observed vs. 14.0 expected. In laborers, production and transport workers, 35 cases were observed vs. 37.0 expected. A further breakdown of these two broad categories into finer subcategories within the major occupational categories revealed no significant excesses. The study, however, is not useful in assessing the risk of STS from exposure to phenoxy acids and/or chlorophenols for several reasons. First, as was pointed out by the authors but subsequently dismissed by them as having not much of an influence, is the possibility that movement from one major occupational category to another over the time period involved for latent conditions to manifest themselves could introduce a negative bias into any estimates of relative risks. The latency for STS was suggested to be a minimum of 15 years (Hueper and Conway, 1964).

The finding of no switching from one occupational category to another that was noted in the "first 20 interviews" in which a change could be noted is not necessarily indicative of fidelity to the same job over long periods in all 408 cases and controls. Information identifying a change may be lacking in those cases and controls if in fact one did occur possibly because of several reasons, for example, separation of the earlier work history from the latter and purging of earlier employment records. Besides the "first 20 interviews" where a change could be noted is not necessarily representative of the entire cohort in any case.

Furthermore, the authors do not know absolutely that any of their cases and controls were exposed to phenoxy acids or chlorophenols or to both since apparently no effort was made to confirm "potential" exposures. Only differences in occupational classification were noted where "potentially" cases or controls could have had exposure to the dioxin-containing herbicides. It was pointed out that the risk estimates noted do not "preclude" the possibility that an association may be found in this study when the cases and controls (or surviving kin) are interviewed for chemical spraying at a later time. The authors themselves concluded that the preliminary study results "should not be taken as substantial evidence against the hypothesis that phenoxy herbicides and chlorophenols may cause human cancer."

The distribution of tumor types differed considerably from the Hardell and Eriksson (1981) study to the Smith et al. (1982b) study. Leiomyosarcomas, malignant histocytomas, neurogenic sarcomas and myxosarcoma seem to predominate in the Hardell and Eriksson (1981) study, whereas fibrosarcomas and liposarcomas appear prominently in the Smith et al. (1982b) study. More attention should be devoted to the study of the distributions of STS types in registry data everywhere in order to determine if such variations in the reporting of STS types are random occurrences. It is possible that the cancer effect of exposure to phenoxy herbicides may be narrowed to just certain types of STSs, the predominant ones in the Swedish studies.

In a later study of STSs, Smith et al. (1983a) conducted a case-control study of STSs in males that were reported to the New Zealand Cancer Registry by Public Hospitals between 1976 and 1980. The author matched one cancer control randomly chosen from the registry with each case, initially starting with 112 of each. Controls were matched for year of registration and by date of birth ± 2 years. Inquiries were made by the authors with the hospital consultant, family doctor, and finally the next-of-kin or patient if alive. Telephone interviews were conducted by only one interviewer, who had no knowledge of the patient's cancer history, and were completed on 80 cases and 92 controls. Because some 32 potential cases (14 ineligible) and 20 controls were excluded or lost from the study for various reasons, it raises a question whether control of confounding by age and year of registration was maintained in the final group of 172 cases and control included in the analysis. Presumably the corresponding "matched" case or control to each of the 52 lost members of the total study group were not excluded. However, since the span of registration was only 5 years, not much age confounding could occur.

Patients were classified as having had potential exposure to phenoxyacetic acids if they had definite, probable or possible exposure to phenoxyacetic acid through spraying or hand contact. The actual chemical was identified only in some instances. The authors concluded in all remaining situations that if the member sprayed "gorse" and/or "blackberries" this was tantamount to potential exposure to phenoxyacetic acid. Smith (1983) calculated elevated but nonsignificant relative risks of exposure to phenoxyacetic acid ranging from 1.3 in those individuals who were "probably exposed" for a minimum of 5 days not in the previous 10 years before cancer registration to 1.6 in individuals "probably exposed" for a minimum of 1 day not in the previous 5 years before cancer registration. When risk ratios were calculated after stratifying by year of birth and whether or not the patient or a relative was interviewed, the rates increased to 1.7 (from 1.6) in the latter and 1.4 (from 1.3) in the former calculation, although still nonsignificant. If the numbers would allow, it would be of interest to repeat the above calculations excluding only those with potential exposure occurring only within the 15-year period just before cancer registration. The small numbers that remain following the 15-year lapse probably precludes such an analysis. Furthermore, the categories of exposure "probably or definitely" exposed for ≥1 day or even 5 days raises a question whether any of the cases or controls could really be said to have ever come in contact with enough phenoxyacetic acid to justify such a designation. It could be that, in fact, potentially exposed individuals in New Zealand have had little or no contact with the herbicide.

The authors did conclude that the finding of a relative risk of 1.7 in individuals with ≥1 day exposure not in the last 5 years cannot be entirely discounted. But then the authors stated that if length of exposure was ≥5 days prior to 10 years before cancer registration, they would expect an increase, and since they do not see an increase, there is no evidence of a "real causal link." One might ask whether this is a suitable criterion for providing evidence of a causal association. Perhaps a more valid group for study would be one where the potential exposure was considerably longer than "5 days" and >15 years before initial cancer registration. As kind of a subtle justification for the finding of no significant risk in workers exposed to phenoxy acids, the author alluded to the fact that there were 500 full-time workers registered in New Zealand who did full-time ground spraying and altogether some 2000 workers who were at some time professionally involved in phenoxyacetic acid herbicide spraying from the air or ground with exposure "very much greater" than that of patients in this study. This kind of argument has appeal if these workers could be shown to have had their exposure sufficiently far in the past that latency considerations could be adequately addressed. However, the real question again remains; how much real exposure did those patients in the study have 10-15 years earlier, and in what numbers. The author remarked that it was surprising that he found no STS victims who had ever worked full-time in phenoxyacetic acid herbicide spraying. Perhaps they have not yet been observed for a long enough period. The time interval of 10 years or 5 years from exposure to registration may not have been long enough to allow latent effects to become evident. However, as was pointed out by the author, the findings do not support the hypothesis that exposure to phenoxyacetic acid herbicides causes STS. But neither do they support a negative finding without better documentation regarding actual exposure and time of actual exposure. Smith (1983), however, noted that his documentation of exposure to 2,4,5-T (and 2,4-D) was at least as good as that in the Hardell and Sandstrom (1979) study, and that although Hardell and Sandstrom (1979) noted higher relative risks of <30 days exposure, Smith (1983) did not. Hence the paradox. Smith (1983) admitted the possibility that 2,3,7,8-TCDD contaminations might be lower in New Zealand as opposed to 2,3,7,8-TCDD contamination in the Swedish studies, although there is no evidence for it. He still maintains that his study showed that exposure to phenoxyacetic acids may not be associated with STS.

Pazderova-Vejlupkova et al. (1981) studied 80 workers involved in the production of 2,4,5-sodium trichlorophenoxyacetate and butylester of trichlorophenoxyacetic acid who subsequently became ill from exposure to 2,3,7,8-TCDD during the period 1965-1968. Only 55 members of this group were followed for 10 years. The remaining 25 either refused to participate or moved leaving no forwarding address. Most patients developed chloracne while 11 developed porphyria cutanea tarda. Chief chemical signs were metabolic disturbances, pathologically elevated lipids with abnormalities in the lipoprotein spectrum, and "pathological" changes in glucose tolerance. Other symptoms noted were biochemical deviations consistent with "a mild liver lesion," light steatosis, periportal fibrosis or activation of Kupffer cells, or nervous system focal damage (peripheral neuron lesion in lower extremities). Altogether six patients were reported to be deceased during this 10-year period, 2 from bronchogenic carcinoma, 1 from cirrhosis, 1 atherosclerosis precipue cerebi and 2 in auto accidents; no STSs or lymphomas were found. Since there was no comparison population with which to estimate relative risk for cancer, the study must be classified at best as clinical with respect to cancer. The 6 deaths (of 55) that occurred during the 10-year observation period cannot be construed to be associated with exposure to the 2,4,5-T. Because of the small number of cases and the short follow-up period, nothing can be said concerning the association of exposure with cancer, especially specific types of cancer such as STS or non-Hodgkin's lymphoma.

Riihimaki et al. (1982, 1983) studied a cohort of 1926 herbicide applicators formed in 1972 from personnel records of four Finnish employers (e.g., the Forestry Authority, Highway Authority, State Railways and a state-owned electric power company). Chlorinated phenoxyacids had been used since the 1950s in Finland for spraying. They constituted 2:1 mixtures of emulsified esters of 2,4-D and 2,4,5-T dissolved in water. Analyses from old herbicide formulations dating back to the 1960s revealed that these mixtures contained 0.1-0.9 mg/kg of 2,3,7,8-TCDD.

This cohort of male workers was exposed a minimum of 2 weeks during at least one growing season from 1955-1971. Follow-up continued 9 years through 1980 for mortality but only until 1978 for morbidity. Fifteen individuals could not be traced by 1980. Expected deaths were generated based upon cause- and age-specific national Finnish death rates for 1975. Expected cases were similarly calculated based upon national incidence rates of 1975.

By 1980, 144 deaths had occurred vs. 184.0 expected, a deficit of 22% in observed mortality. Only 26 cancer deaths had occurred vs. 36.5 expected, a 29% deficit. The authors separated out "natural" deaths from the total. The observed residual deaths equaled 39 while the expected deaths equaled 28.7. This excess was of borderline significance. The authors also considered 10-year and 15-year latent periods. Even after 15 years, the deficit of deaths continued to manifest itself both in categories of all causes and total cancers; 35 observed vs. 53.6 expected and 5 observed vs. 11.3 expected, respectively. Similarly, the 7-year follow-up of cancer morbidity revealed 26 cases of cancer vs. 37.2 expected. After a 10-year latent period, 16 cancer cases were observed vs. 20.1 expected. None of the 26 cancer deaths or 26 cancer cases were of the STS or lymphoma type. (However, only 0.1 STS and 0.5 lymphomas were expected.) In no instance was cancer of any site significantly elevated.

The authors noted that this unusual deficit of mortality and morbidity of between 70 and 82% (even after 15 years from initial exposure) was probably a consequence of the "healthy worker effect" in that only able-bodied and healthy individuals were selected into the industry. The fact that the cohort was assembled in 1972 from records of persons who were exposed as early as 1955 (17 years prior) raises the likelihood that in 1972 a "survivor" population remained (45 deaths before 1972 were eliminated from the cohort) that was relatively healthy. Furthermore, the unusually large number of not "natural" expected and observed deaths (probably accidents and external causes) occurring to this cohort indicate a relatively youthful population was under scrutiny. The leading cause of death to persons under 35 years is from accidents, based on national vital statistics.

The authors correctly noted that, because of limitations in the study material, only powerful carcinogenic effects could be detected. Risk ratios higher than 1.5 for all cancers, 4.0 for lymphomas and 10.0 for STS could be excluded based on this data set from the authors' own calculations. More follow-up is needed in order to provide a stable assessment of the relationship between exposure and cancer. The authors concluded that this study will allow no assessment of STS because "the number of persons having a sufficiently long latency period is too small." It was suggested that more valid conclusions could be made only with the passage of time (Riihimaki et al., 1983).

Recently, the Michigan Department of Public Health (1983b) produced an ecological study of soft and connective tissue cancer mortality rates in Midland and other selected Michigan counties. They found that mortality rates for this cause were 3.8-4.0 times the national average for the periods 1960-1969 and 1970-1978, respectively, for white females in Midland. These estimates are based upon 5 deaths and 7 deaths, respectively, and are listed in Table VI-5. No excess risk was reported among white males, however. The Michigan Department of Health concluded that because of the occurrence of these two successive elevated rates, it is unlikely to be a chance happening. At the same time the age-adjusted male and female cancer mortality rates for Midland were below that of the State of Michigan for the period 1970-1979. Midland County is the home of a major chemical company that produced phenoxyacetic acid herbicides until recently. The authors stated that a detailed review of death certificates, hospital records, residency and occupational histories of the 20 male and female cases revealed no "commonalities" that suggest a "single causative agent," although a majority or their spouses had worked at this chemical facility. They recommend that a case-control study should be employed to evaluate possible influences, such as lifestyle, occupation or location of residence on the risk of STS.

In a series of reports prepared under the auspices of the U.S. Air Force, Wolfe et al. (1984) completed the first phase of a study of Air Force personnel involved in the aerial dissemination of TCDD-containing herbicides in the Republic of Vietnam (RVN). During the period of time beginning in 1962 and ending in 1971, ~1278 male Air Force personnel (Ranch Handers) were identified as having been involved in the effort to 1) defoliate vegetation in Vietnam in order to decrease the risk of ambush and 2) destroy enemy crops (Wolfe et al., 1985). Based on a 1984 report of baseline mortality study results (Wolfe et al., 1984), the cohort involved in the mortality

TABLE VI-5

Midland County Soft and Connective Tissue Cancer Deaths 1960-1981*

Identification			Type, Site and Progression of Malignancy			Month and Year Diagnosed
Year of Death	Sex	Age	Type	Primary Site	Metastases	
1961	F	24	Hemangiosarcoma	Face	Skull and upper lobe of lung	5-58
1963	F	75	Liposarcoma	Right gluteal	Unknown	Unknown
1964	F	51	Leiomyosarcoma	Uterus	Widespread	11-63
1968	F	37	Liposarcoma	Spine	Lungs, pelvis	1-66
1969	F	45	Fibrosarcoma Leiomyosarcoma	Right thigh Uterus	Lung, liver Adrenal gland and skin	10-68
1970	F	59	Kaposi sarcoma	Right leg	Lymph nodes	8-68
1970	F	56	Fibrosarcoma Leiomyosarcoma	Right thigh Abdominal wall	Spine Lung	1960 1967
1974	F	1	Rhabdomyosarcoma	Inguinal area	Unknown	8-73
1976	F	77	Liposarcoma	Right thigh	Buttock, lung, rib, lymph nodes	12-74
1978	F	64	Leiomyosarcoma	Left knee	Liver, lymph nodes, lung, bone	7-70

TABLE VI-5 (cont.)

Identification			Type, Site and Progression of Malignancy			
Year of Death	Sex	Age	Type	Primary Site	Metastases	Month and Year Diagnosed
1978	F	26	Rhabdomyosarcoma	Rectum	Lung, neck, inguinal region	6-76
1978	F	88	Fibrosarcoma	Right cheek	Facial area	6-78
1979	F	27	Leiomyosarcoma	Left thigh	Lung	3-78
1962	M	63	Rhabdomyosarcoma	Left lower leg	Lung and right outer chest wall	8-61
1967	M	77	Mesothelioma	Lung	Lung, peritoneum and diaphragm	6-67
1967	M	20	Rhabdomyosarcoma	Pharynx	Periorbital area and liver	1-67
1969	M	32	Liposarcoma	Left arm	Perineum and buttock	6-64
1971	M	76	Leiomyosarcoma	Small intestine	Liver	10-69
1972	M	89	Leiomyosarcoma	Retro-peritonal region	Hepatic system	7-72
1976	M	53	Fibrosarcoma	Peritioneum	Lung, liver	3-75

*Source: Adapted from Michigan Department of Public Health, 1983b study was smaller at 1256 because of the exclusion of 22 killed in action and was divided into three main occupational categories as follows:

1. Officers (pilots, navigators and others)	466
2. Enlisted (flight engineers)	206
3. Enlisted (others)	584
TOTAL	1256

The authors categorized the Ranch Handers as having had "exposure" to the TCDD-containing herbicides if they were involved in the aerial spraying of the herbicides. They were matched to 6171 cargo mission air crew members and support personnel generally on a 5 to 1 basis according to similarity of training and military background experiences, occupation and race. The comparison population presumably had no exposure to TCDD. In an earlier 1983 report (Lathrop et al., 1983), 50 deaths were identified in the study group versus 250 in the comparison population. Of these 50 deaths, 23 were due to external causes, 4 were malignant neoplasms, 16 were circulatory causes, 5 were digestive disorders and 1 was an endocrine disorder.

In the later December 1984 update, Wolfe et al. (1984) added 4 more deaths to the study population for a total of 54 deaths occurring to Ranch Hands while adding 15 to the 250 that had already occurred in the comparison group through December 31, 1983. Altogether this update produced a total of 6 cancer deaths in the Ranch Hands versus 43 cancer deaths in the comparison population. The greatest cause of death in both Ranch Handers and the comparison population were accidents with 19 and 94, respectively. None of the 6 cancer deaths and 1 of the 43 deaths in the comparison group were

STSs. Comparison of overall mortality in the Ranch Handers with other Air Force military personnel was nearly identical (~4.3%). Ranch Hand ground enlisted personnel suffered somewhat greater (although not significant) mortality than did Ranch Hand officers. Comparison of mortality in the Ranch Handers with other groups such as U.S. white males, Department of Defense retired enlisted men, U.S. civil servants, active duty Air Force and West Point officers from the class of 1956, were similar except for Air Force active duty officers who exhibited significantly less mortality. The authors attribute this to higher health qualification standards.

There were few biological markers that might tend to support the assumption that Ranch Hands were exposed to 2,3,7,8-TCDD. In the Banbury report, Lathrop et al. (1984) reported that the dermatologic evaluation revealed no cases of chloracne through clinical diagnosis or bioassay. A questionnaire analysis of acne in Ranch Handers and comparison groups showed no unusually different incidence, severity, duration or distribution of anatomical locations in either group. Lathrop et al. (1984) said in fact that the "historical occurrence of chloracne was highly unlikely in the Ranch Handers".

This study suffers from several deficiencies that limit its usefulness in a determination of human health effects, notably cancer, and especially STS from exposure to 2,3,7,8-TCDD-contaminated phenoxy herbicides. First, it is basically a study of young men who were involved in the Air Force aerial spraying missions. This is evidenced by the exceptionally large number of accidents attributable to members of the cohort. It is the largest single cause of death in these men. Because this is a young group it is unlikely that substantial mortality will occur to the cohort until many more years of follow-up have passed. In fact, even after 15 years following initial exposure <5% of the cohort have died. Since most cancers have a latency of ≥15 years following initial exposure it is not likely that a cancer risk from 2,3,7,8-TCDD, if any, will manifest itself for some time.

Furthermore, the relatively rare STS, which is thought to have an even longer latency period, may not appear as a risk in this cohort until well after the 20th year. Additionally, this cohort exhibits little evidence of actual exposure to the herbicide in question, thus raising the possibility of misclassification. In other small cohort studies (Cook et al., 1980; Ott et al., 1980; Zack and Suskind, 1980) substantial numbers of the study cohorts exhibited evidence of exposure to 2,3,7,8-TCDD as indicated by the presence of chloracne, a clear biological marker. Few of the Ranch Handers exhibited evidence of this condition (Lathrop et al., 1984). In fact, as was suggested by the authors, the historical occurrence of chloracne was considered highly unlikely in the Ranch Hands. Neither do they present convincing evidence of other conditions suggestive of an association with exposure to the dioxin-containing herbicide that cannot be explained by confounders, according to the authors. In fact Ranch Handers, who were heavily populated with officers, pilots, navigators and flight engineers, may not have been as heavily exposed to the phenoxy herbicides as other U.S. military personnel in Southeast Asia. Perhaps Army combat foot soldiers or the non-Ranch Hand personnel who did the spraying on the ground around the military bases would constitute a more appropriate cohort for study. Lathrop et al. (1984) concluded that the absence of any association of "clinical endpoints" with herbicide exposure must be viewed as insufficient evidence supporting a cause-and-effect relationship. But this absence of any "clinical endpoints" might also indicate evidence of a lack of exposure to the phenoxy herbicides in question by the Ranch Handers. This study must be viewed as inadequate in assessing the risk of cancer from exposure to 2,3,7,8-TCDD-containing phenoxy herbicides.

In a separate review of the epidemiological evidence for STS from exposure to 2,4,5-T-containing herbicides, the United Kingdom Ministry of Agriculture, Fisheries and Food (1983) concluded that there was no evidence to recommend altering their earlier conclusion that formulations of phenoxy acid herbicides and related wood preservatives as "presently cleared" are safe and may continue to be used. This report readily discounts the positive studies of Hardell and Eriksson (1981) as being biased, and it makes no reference to the later validity study by Hardell (1981) of his own work utilizing colon cancer controls. In this report Hardell answered these early criticisms that were reiterated by the British in their report. At the same time, the British report appears to put undue emphasis on nonpositive studies that do not demonstrate a risk, although most of them have methodological limitations (e.g., low power, insufficient latency and inappropriate study methods). In short, the British review appears to be overly optimistic about the safety of 2,4,5-T herbicides.

Fingerhut et al. (1984) recently completed a review of medical and available exposure records of seven U.S. chemical workers that had been diagnosed as having STS and who were reported to have had possible exposure to dioxin. These cases collectively produced a clustering effect of the relatively rare STSs among former employees of a portion of the U.S. chemical industry where exposure to compounds contaminated with 2,3,7,8-TCDD is most likely to have occurred. Fingerhut et al. (1984) reported that a subsequent review of the Armed Forces Institute of Pathology and a review of one of the authors of the Fingerhut paper confirmed the diagnosis of 5 of the 7 U.S. chemical workers as STSs.

In terms of occupational exposure, Fingerhut et al. (1984) proposed a strict definition of exposure as follows: a record must exist somewhere that shows an assignment to either a 2,4,5-T department or to a trichlorophenol department at some time in the past. If such a record did not exist, then the individual would not have been considered to have had a confirmed exposure. Four of the seven who had a confirmed exposure in this manner were also members of cohorts that had been studied previously, while the remaining three could not be confirmed as having been assigned to any 2,4,5-T department or trichlorophenol department. The latter three were not identified as having been part of any earlier study but were case reports of Johnson et al. (1981) and Moses and Selikoff (1981). Individuals who were members of study cohorts of "exposed individuals" might be expected to have better documentation of exposure, based upon employment records, than would cases turning up in a medical practice.

However, Fingerhut et al. (1984) pointed out that of these three cases, one worked 32 years in production, clerical, truck driving and maintenance jobs in a chemical manufacturing site that produced trichlorophenol and 2,4,5-T; the second worked 2.5 years as a production worker in a plant that made 2,4,5-T; and the third was a production and maintenance worker for 29 years at the same facility as the second worker. It would seem that the opportunity for exposure to 2,3,7,8-TCDD containing 2,4,5-T or trichlorophenol must be considered a distinct possibility in the first two cases, especially since both were involved with maintenance for many years.

Johnson et al. (1981) pointed out that the second case could not have satisfied a minimum latency requirement for exposure to TCDD since his 2.5 years as a production worker occurred just before his diagnosis and death. However, this man's father was employed with this same plant almost as long as his son was alive and it seems plausible that because of this connection the son may have been exposed.

One must have reservations about the usefulness of a classification scheme that relies on documentation of an assignment to a specific area of a plant as proof of exposure to dioxin without real evidence substantiating that exposure (i.e., either biological or physical measurements), while at the same time assignment to all other areas of the same plant is considered insufficient evidence of exposure although nothing is offered to substantiate the presence or lack of exposure to 2,3,7,8-TCDD in either case. In most occupational prospective cohort epidemiologic studies, employment at a plant where the suspect agent is produced or found has been considered sufficient enough to call such a person "exposed" and thus included in a cohort for study. On the other hand, if the Fingerhut et al. (1984) definition were retrospectively applied to the already small occupational cohorts from which the first four STSs came, even two of these relatively rare STSs could conceivably constitute an excessive risk in the much smaller cohorts circumscribed by their definition. Fingerhut et al. (1984) agreed that an excess risk of STS would remain even with just two confirmed cases, and hence the possibility of a causal relationship between exposure to 2,3,7,8-TCDD and the development of STSs cannot yet be ruled out.

In summary, the associations reported in the two Swedish soft-tissue sarcoma studies are strong enough to make it unlikely that they have resulted entirely from random variation bias or confounding, even though the possibility cannot be excluded. These studies provide a strong suggestion that phenoxyacetic acid herbicides, chlorophenols or their impurities are carcinogenic in humans.

Malignant Lymphomas -- A separate series of clinical observations at the Department of Oncology in Umea, Sweden (Hardell, 1979), led the researchers to conduct a case-control study of malignant lymphoma in relation to phenoxyacetic acid, chlorophenols, and other organic compounds (Hardell et al., 1980, 1981). Approximately 33% of the cases in this study were patients with Hodgkin's disease; the remainder of the cases were non-Hodgkin's lymphomas.

This study employed essentially the same methods and produced results comparable with those of the STS studies: statistically significant 5-fold to 6-fold relative risks in relation to phenoxyacetic acids and chlorophenols were confirmed. In addition, an elevated relative risk was found in connection with exposure to organic solvents, such as benzene, trichloroethylene, and styrene. In the published report, the methods and results were incompletely documented, especially the possibility of confounding by exposure to the organic solvents.

In the update of the earlier 1980 study, Hardell et al. (1981), utilizing the same basic data source, found that 36.1% of the cases had been exposed to phenoxy herbicides or chlorophenols, while only 9.6% of their controls were so exposed. The estimated relative risk was 6.0 when matching was considered and 5.3 when matching was eliminated. When cases and controls that were exposed to chlorophenols only were excluded, the relative risk of lymphoma from phenoxy acids alone was 4.8 (95% C.I. 2.9-8.1). On the other hand, if exposures to phenoxy acids are excluded and consideration is given to just chlorophenols (which includes combined exposure to phenoxy acids and chlorophenols), then the relative risk equaled 4.3 (95% C.I. 2.7-6.9). The author further subdivided this group into "low-grade" vs. "high-grade" exposures to chlorophenols. A continuous exposure of not more than 1 week or repeated intermittent exposures totaling not more than 1 month was classified as low-grade. The relative risk for high-grade exposure was 8.4 (95% C.I. 4.2-16.9), while that for low-grade exposure equaled 9.2 (95% C.I. 1.6-5.2). If exposure to organic solvents is examined, given that cases and controls exposed to only phenoxy acids and/or chlorophenols were excluded except for combined exposure to organic solvents, it is found that high-grade and low-grade relative risks were 2.8 (95% C.I. 1.6-4.8) and 1.2 (95% C.I. 0.5-2.6), respectively. However, the author noted that exposure to phenoxy acids and high-grade organic solvents (exposure to chlorophenols excluded) produced a relative risk of 11.2 (95% C.I. 3.2-39.7) based upon a few cases and controls with exposure to both. The authors concluded that "exposure to organic solvents, chlorophenols and/or phenoxy acids constitutes a risk factor for malignant lymphoma."

The Hardell et al. (1981) study is still subject to the same methodological criticisms to which the earlier study was subjected. Chief among those is the possibility of observational and/or recall bias creeping into the responses that are elicited from self-administered questionnaires on kind and length of exposure. Secondly, confounding by exposure to potentially carcinogenic organic solvents and other agents could have had an effect on the risk estimate, although Hardell (1981) insists that they did not.

Other research has tentatively suggested that lumberjacks may be at increased risk of lymphoma (Edling and Granstam, 1979). The Nitro study found three deaths from cancers of the lymphatic and hematopoietic system, against only 0.88 expected (p=0.06, one-tailed Poisson test).

The lymphoma case-control study (Hardell et al., 1980, 1981) is consistent with the two STS studies discussed above. On the other hand, the consistency could also reflect an (as yet) unidentified common flaw in all these studies.

The two Swedish case control studies on STSs and a later case control study of malignant lymphoma (Hardell et al., 1981) were subjected to a validity analysis with respect to the assessment of exposure by Hardell and Eriksson (1981). To answer the question raised regarding the recall of occupation in a forestry/agriculture job, secondary to the recall of exposure to phenoxy acids and/or chlorophenols, the cases and controls were divided into three groups: those who worked their entire time since 1950 in an agriculture/forestry job; those who worked some time in an agriculture/forestry job but not exclusively; and the remainder who never worked in a forestry/agriculture job. The study found that the risk ratio was still 8.2 for STS in exclusively agriculture/forestry workers who were exposed to phenoxy acids compared with workers found in other occupations having no apparent exposure to phenoxy acids or chlorophenols. Even when comparing phenoxy acid- and/or chlorophenol-exposed agricultural/forestry workers exclusively with nonexposed agricultural/forestry workers, the risk ratio was still 7.1. This argument seems to answer effectively questions regarding recall of occupation secondary to exposure.

On the other hand, the relative risk remains 5.4 when comparing phenoxy acid and/or chlorophenol exposed workers exclusively in occupations other than agriculture/forestry with nonexposed workers in those same occupations, thus, suggesting the presence of either recall bias or still another occupation with potential exposure to phenoxy acids and/or chlorophenols (Table VI-6).

When woodworkers are separated out (possible exposure to chlorophenols in treatment of wood) the risk ratio becomes 9.7 (Table VI-7). These data suggest the presence of some recall bias.

Another focus of the Hardell and Erikkson (1981) study was to determine if observational bias on the part of the investigators could explain the

TABLE VI-6

Other Occupations (Minus Forestry/Agriculture)*

Group	Phenoxy Acids/Chlorophenols	Non-exposed
Cases	11	68
Referents	5	167
	RR = 5.4	X^2 = 11.01 ($P<0.01$)

*Source: Hardell and Erikkson, 1981

RR = Relative risk

TABLE VI-7

Other Occupations (Minus Forestry/Agriculture/Woodworkers)*

Group	Phenoxy Acids/Chlorophenols	Non-exposed
Cases	4	66
Referents	1	160
	RR = 9.7	$X^2 = 5.98$ ($P<0.05$)

*Source: Hardell and Erikkson, 1981

RR = Relative risk

significantly high risk estimates. To answer the question, the study compared the exposure data derived from the interviewee's returned questionnaires only with the combined information from both the phone interviews and questionnaires. The study found no substantial differences in the frequency of reporting exposure.

Still a third consideration of possible bias involves recall of exposure to phenoxy acids and/or chlorophenols because of subject knowledge of having cancer in the cases versus no knowledge of cancer in the referent population. The study chose as a referent group for the 52 STS cases (Hardell and Sandstrom, 1979) and the 169 malignant lymphomas (Hardell et al., 1981) a group of 154 colon cancer cases from the same population source and compared their exposure to phenoxy acids and/or chlorophenols by broad age groupings, and by rural vs. urban residence.

Utilizing a Mantel-Haenszel rate ratio, the study found the risk of exposure to phenoxy acids remaining significantly high at 5.5 and to chlorophenols 5.4 in the STS cases compared with the colon cancer controls. Similarly, with the malignant lymphomas, the identically derived risk ratios remain significantly high at 4.5 with respect to phenoxy acids and/or chlorophenol exposure in the cases, hence, the study concludes, no "substantial observational bias" exists. If it is assumed in this study that recall bias was and is the same as observational bias, then such a conclusion may not be entirely warranted from the comparison. Certainly, it appears that no recall bias existed because of subject "knowledge of having cancer" based on the authors' analysis. But it does not rule out the possibility that recall bias can still be present in their data for other reasons.

Hardell et al. (1981) refers to an intense "debate about phenoxy acids and their presumptive risk" in Sweden at the time the colon cancer study was conducted. But, there is no reason to think that colon cancer victims would assume their disease was brought about from exposure to dioxin containing chemicals if no connection was suggested.

It seems plausible that STS and non-Hodgkin's lymphoma patients would either learn at the time of their diagnosis that exposure to dioxin-containing chemicals was the likely cause of this rare type of tumor or quickly learn from other sources, such as the news media, that exposure to herbicides containing dioxin could cause this rare form of cancer whereas colon cancer victims (a rather common form of cancer) would not necessarily be led to believe that exposure to the same dioxin-containing chemicals caused their disease. Hence, it is not difficult to imagine that such unusual victims of cancer could better "remember" exposure to such chemicals than could colon cancer patients.

Therefore, although the Hardell (1981) study may explain any biases introduced from secondary recall of occupation, observational bias introduced from the telephone interviewer and recall bias based on subject knowledge of cancer, it does not adequately answer questions of recall bias introduced through the acquired awareness on the part of the victim of STS or non-Hodgkin's lymphoma that his condition may have been caused by exposure to dioxin-containing herbicides.

Stomach Cancer -- Studies of two of the oldest cohorts of workers known to have been exposed to 2,3,7,8-TCDD containing phenoxyacetic acid herbicides report stomach cancer mortality rates significantly higher than expected. The results in each study were based on small numbers of deaths. In one study (Axelson et al., 1980), 348 Swedish railroad workers with at least 46 days of herbicide exposure between 1955 and 1972 were followed through October 1978. The workers were grouped on the basis of their primary herbicide exposures: those primarily exposed to phenoxyacetic acids (2,4-D and 2,4,5-T) only, to amitrole (aminotriazole) only, and to both types of herbicides. After a 10-year latency was achieved, 3 stomach cancer deaths were observed vs. 0.71 expected ($p<0.05$). None were attributable to amitrol alone, but two were assigned to phenoxy acids alone while the remaining stomach cancer death occurred in a worker exposed to both amitrol and phenoxy acids. The excess was more pronounced (3 observed vs. 0.57 expected, $p<0.05$) among those with early exposure (1957-1961) to phenoxy acids and/or amitrol. If persons who were exposed to just amitrol alone are excluded, thus leaving individuals exposed to phenoxy acid alone and amitrol in combination, the excess is enhanced further (3 observed vs. 0.41 expected, $p<0.01$).

Axelson et al. (1980) also noted an excess in total "tumors" after 10 years latency as well (15 observed vs. 6.87 expected, $p<0.005$). This is pronounced in those exposed early to phenoxy acids alone (6 observed vs. 2.60 expected, $p<0.01$) and phenoxy acids in combination with amitrol (5 observed vs. 1.34 expected, $p<0.05$). Presumably, "tumors" in Sweden are analogous to malignant neoplasms in the United States. The author states that no specific type of tumor predominates and no breakdown by tumor type is provided.

The other study showing increased stomach cancer mortality is the follow-up of 75 workers exposed to 2,3,7,8-TCDD during and after a 1953 runaway reaction at a trichlorophenol manufacturing facility in Ludwigshafen, Federal Republic of Germany (Thiess and Frentzel-Beyme, 1977). Two sources were used to calculate expected deaths: national mortality rates for the period 1971-1974, and 1972-1975 rates for Rhinehessen-Palatinate, the region in which Ludwigshafen is located.*

The results, shown in Table VI-8, indicate an increased rate of stomach cancer mortality that also is not likely to have been due to chance alone.

Two aspects of the methodology used could have influenced these results. First, the available report does not include an analysis allowing for a minimum period of cancer induction. All three stomach cancer deaths in the Ludwigshafen cohort occurred more than 10 years after initial exposure. Employing a 10-year restriction to follow-up (as in the Swedish cohort study) would result in a higher relative risk estimate by reducing the number of expected deaths.

Secondly, national and regional mortality rates from the 1970s were used to generate expected deaths to compare with observed mortality over a much longer period (1953-1977). The substantial decline in stomach cancer mortality in West Germany during the late 1950s and 1960s would likely make these expected figures too large.

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*The report originally included expected deaths using rates for the city of Ludwigshafen, which were later shown to be inaccurate.

TABLE VI-8

Analysis of Stomach Cancer Mortality in a Group of West German Factory Workers Exposed to 2,3,7,8-TCDD*

Source for Expected Deaths	Stomach Cancer Deaths		Relative Risk	Significance Level
	Observed	Expected		
Federal Republic of Germany 1971-1974	3	0.559	5.4	0.02
Rhinehessen-Palatinate 1972-1975	3	0.495	6.1	0.01

*Source: Thiess and Frentzel-Beyme, 1977

The researchers also used an internal control group that does not raise the second concern discussed above. This group consisted of 75 men, each matched to study group members by age and date of entry into employment, and selected at random from a list of over 10,000 persons who had been included in previous cohort studies by the same investigators. No stomach cancer deaths occurred in this control group during the follow-up period. Thus, use of the internal control groups also indicates an excess of stomach cancers in the exposed workers.

In an update of this earlier study, Thiess et al. (1982) continued the follow-up of his cohort through 1979 by adding 2 additional years of follow-up and apparently reducing the size of his cohort from 75 to 74. Altogether 21 deaths (4 more than from the earlier study) occurred vs. 18 and 19 deaths in the 2 matched (1 to 1) internal comparison groups. With respect to cancer deaths, the numbers were respectively 7, 5 and 5. The first control group was manually matched from the total number of persons (5500 included in the cohort until the end of 1976) and the second, at random, by computer for some 8000 employees. In addition, 19 expected total deaths were estimated based on 1970-1975 mortality statistics of Rhinehessin-Palatinate, 18 expected deaths based on 1970-1975 mortality statistics of Ludwigshafen, and 20 expected deaths based upon 1971-1974 mortality statistics of the Federal Republic of Germany. Just as in the earlier study, the three stomach carcinomas noted earlier appear to be significantly elevated regardless of which external comparison group is used (Table VI-9).

On the other hand, one stomach cancer appeared in the randomized internal control group. None appeared in the manually matched internal control.

TABLE VI-9

Reanalysis of Stomach Cancer Mortality in a Group of West German Factory Workers Exposed to 2,3,7,8-TCDD*

Source for Expected Deaths	Stomach Cancer Deaths		Relative Risk	Significance Level
	Observed	Expected		
Federal Republic of Germany 1971-1974	3	0.7	4.3	0.034
Rhinehessin-Palatinate 1970-1975	3	0.64	4.7	0.027
Ludwigs-Shafen 1970-1975	3	0.61	4.9	0.024

*Source: Thiess et al., 1982

No other elevated risks for any other cause were evident and no STSs appeared. When latency was considered only, the risk of stomach cancer remained significantly elevated after a lapse of 10 years (3 observed, 0.52 expected, p<0.016) and then after a lapse of 15 years (2 observed, 0.23 expected, p<0.02) based upon death rates of Rhinehessin-Palatinate, 1970-1975.

Again, these study conclusions are limited by the small size of the study group and the very few cancer deaths noted at any particular site. Thus, it is insensitive to the detection of a significantly elevated risk for most causes of cancer, especially STS and lymphomas. Although, stomach cancer is elevated significantly, it is based only upon three deaths and since one stomach cancer death has been noted in an internal control group in the updated version, it appears that this finding has been weakened somewhat. Furthermore, as was pointed out earlier, trends in stomach cancer mortality during the 1950s, 1960s and 1970s could make the comparison of stomach cancer mortality with expected deaths less valid based upon 1970-1975 rates.

In summary, the evidence that phenoxyacetic acids and/or 2,3,7,8-TCDD might increase the risk of stomach cancer consists of two studies, each of which reports a statistically significant excess that is based on only three stomach cancer deaths. Further follow-up of these and similar cohorts is warranted, but firm conclusions cannot yet be made.

Four additional cohort studies have reported results that do not show increased stomach cancer mortality rates in groups of workers exposed to phenoxyacetic acids and/or 2,3,7,8-TCDD. These are studies of 2,4,5-T production workers in Midland, Michigan (Ott et al., 1980), Finnish phenoxyacetic acid herbicide applicators (Riihimaki et al., 1978), the Nitro study in which workers were exposed to 2,3,7,8-TCDD (Zack and Suskind, 1980) and trichlorophenol manufacturing workers (Cook et al., 1980).

As previously mentioned, the Nitro study included a single death from STS and a weakly suggestive increase in lymphatic and hematopoietic system cancer mortality. The Midland study of 204 workers included only one cancer death, a tumor in the respiratory system. In the Finnish study, histologic information on tumor types was not provided; however, there were no deaths from lymphoma.

The results pertinent to stomach cancer mortality in the three studies are shown in Table VI-10. Results of neither the Midland study nor the Nitro study contradict the findings of the Swedish and West German investigations previously discussed. This can be shown in two ways. First, the upper 95% confidence limits for the relative risk estimates from these two "negative" studies exceed even the highest point estimates of relative risk (6.1) from the two "positive" studies (see Table VI-7).

This indicates that the relative risk estimates from the Midland and Nitro studies, even though equal to zero, are nevertheless not significantly different from the estimates of 6.1, given the sample sizes, follow-up periods, age distribution and comparison group rates.

TABLE VI-10

Stomach Cancer Mortality in Three Studies of Workers Exposed to Phenoxyacetic Acid Herbicides and/or 2,3,7,8-TCDD

Stomach Cancer Deaths		Relative Risk	95% Confidence Interval	Reference
Observed	Expected			
0	0.14[a]	0	0-26.3	Ott et al., 1980
5	6.9[a,b]	0.7	0.2-1.7	Riihimaki et al., 1978
0	0.5[b]	0	0-7.4	Zack and Suskind, 1980

[a] Estimated from total cancer expected deaths (see footnote in text).

[b] Entire follow-up period without regard for minimum time for cancer induction (Ott et al., 1980 used a 10-year minimum induction period).

In addition, the smallest detectable relative risk in the Midland study ($\alpha = 0.05$, $\varphi = 0.2$ one-tailed Poisson test) was 21.4 (3 observed deaths, 0.14 expected).* Similarly, the smallest detectable relative risk in the Nitro study ($\alpha = 0.05$, $\varphi = 0.2$, one-tailed Poisson test) was 10.0 (5 observed deaths, 0.5 expected). This calculation is based on results for the entire follow-up period. If, as in the Midland study, a minimum period of cancer induction had been employed, the expected deaths would have been fewer and the smallest reasonably detectable relative risk would have been greater. This analysis of statistical power indicates that the Nitro and Midland studies had very low probabilities of detecting the ~6-fold increases in risk suggested by the Swedish and West German investigations.

Statistically, the study of Finnish herbicide applicators is inconsistent with the results of the Swedish and West German cohort studies. The smallest reasonably detectable relative risk ($\alpha = 0.05$, $\varphi = 0.2$, one-tailed Poisson test) was only 3.1 (11 observed deaths, 3.6 expected).† The study, therefore, appears powerful enough to detect relative risks even smaller than those seen in the Swedish and West German studies. A partial explanation for this apparent inconsistency could lie in the fact that the

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*Ott et al. (1980) did not report expected deaths from stomach cancers. The figure 0.14 was obtained by multiplying the numbers of expected deaths from all cancers (2.6, allowing a 10-year minimum induction period) by the percentage of stomach cancers among the expected deaths in the Nitro study (0.5/9.04 = 5.5%). The two studies used United States white male mortality rates and covered similar calendar years in follow-up (1949-1978 in Nitro and 1950-1976 in Midland), but a similarity in age distributions cannot be established from the published reports.

†The expected stomach cancer deaths were estimated in the same manner as for the Midland study. A proportion of 20% of all cancer deaths was applied because Finnish male mortality rates are known to be very high.

Finnish study set the minimum period of herbicide exposure for membership in the cohort at 10 days (2 working weeks) and noted that the "total strength of exposure has, in most cases, been a few weeks only." The Swedish study of herbicide applicators set the minimum exposure at 46 days (>1 spraying season).

There are also certain inconsistencies in the data from the Finnish study that the authors note but find difficult to explain. In particular, no cancer deaths occurred during the latter part of the study period among Forestry Authority workers (1 of 4 groups included in the cohort), even though 9.0 deaths were expected. This finding strongly suggests some deficiency in follow-up or in the source records from which vital status was determined.

In summary, four cohort studies of workers exposed to phenoxyacetic acid herbicides and/or 2,3,7,8-TCDD do not report increased risks of stomach cancer. Only one of these, however, was statistically powerful enough to be inconsistent with the two studies that tentatively suggest an increase in stomach cancer risk. The available report of this study of Finnish herbicide applicators contains methodologic questions that require clarification.

Case Reports and Epidemiologic Studies on Teratogenicity and Reproductive Effects. A positive association between 2,4,5-T exposures and increases in birth defects or abortions has been reported in human populations in Oregon (U.S. EPA, 1979b), New Zealand (Hanify et al., 1981), and Australia (Field and Kerr, 1979). A lack of any such association has been reported in human populations in Arkansas (Nelson et al., 1979), Hungary (Thomas, 1980), New Zealand (Dept. of Health, New Zealand, 1980; McQueen et al., 1977), and Australia (Aldred, 1978). Almost all of the reports are geographic correlation studies, and because of the uncertainties inherent in this type of epidemiologic investigation, as well as the difficulties in distinguishing the effects of 2,4,5-T from those of 2,3,7,8-TCDD contamination, none of the reportedly positive associations unequivocally identify either 2,4,5-T or 2,3,7,8-TCDD as the causative agent. Similarly, the reportedly negative associations do not rule out 2,4,5-T or 2,3,7,8-TCDD as potential teratogens or abortifacients in humans.

Based on a report of a high incidence of abortions in a small group of women living around Alsea, Oregon, who may have been exposed to the herbicide 2,4,5-T from aerial spraying (Smith, 1979), the U.S. EPA (1979b) initiated a study, often referred to as the "Alsea II study," to determine if spontaneous abortion rates differed between the exposed and unexposed populations, if spontaneous abortion rates evidenced seasonal variation in these two groups, and if such seasonal variations were associated with 2,4,5-T spray application.

The Spontaneous Abortion Rate Index, as defined by the U.S. EPA, is "basically the ratio of the number of hospitalized spontaneous abortions to the number of births corresponding to the spontaneous abortions, based on the residence zip code of the women contributing to each event." Upon completion of the study, the U.S. EPA concluded that (1) the 1972-1977 Spontaneous Abortion Rate Index for the study area was significantly higher than in the Rural Control Area or the Urban area; (2) there was a statistically significant seasonal cycle in the abortion index in each of the areas with a period of ~4 months. In particular there was an outstanding peak in the study area in June; and (3) there was a statistically significant correlation between the Spontaneous Abortion Rate Index and spray patterns in the study area when a lag-time of 2 or 3 months was included. The U.S. EPA concluded, however, that "This analysis is a correlational analysis, and correlation does not necessarily mean causation."

Milby et al. (1980), citing three critiques of the Alsea II study (not published in the open literature), state that the statistical method and basic design of the Alsea II study were sufficiently flawed to make this study of no use in human risk assessment. The Alsea II study has also been reviewed by a panel of scientists who, in a published report of their meeting, also concluded that the basic design of the study was inadequate to demonstrate either an effect or absence of an effect of exposure to 2,4,5-T (Coulston and Olajos, 1980). The major inadequacies of the study were that the data collection methods were likely to result in the underestimation of abortions, particularly in the urban area (the incidence of abortions in all three groups was within the expected background rate of 8-15%); only a small part of the area from which the exposed subjects were selected was actually sprayed with 2,4,5-T, and the study was not controlled for other factors such as age, smoking habits and alcohol consumption, which may affect the spontaneous abortion rate. Based on a new report by Smith (1979), the U.S. EPA is attempting or has attempted to correlate 2,3,7,8-TCDD levels in the affected areas with the observed rate of abortion. No published reports have been located on the outcome of this effort.

Nelson et al. (1979) noted a general increase in the reported incidence of facial cleft in both high and low exposure groups in Arkansas from 1948-1974. In this study, exposure estimates were based on average rice production in different areas of Arkansas, and the incidence of cleft palate was determined by screening birth certificates and checking records of the Crippled Children's Services. No consistent exposure/effect correlations were noted, and the general increase with time in the incidence of facial clefts was attributed to better reporting procedures; however, there does not have to be a direct correspondence of malformations in human beings and experimental animals.

Of the four reports available from New Zealand (Dept. of Health, New Zealand, 1980; McQueen et al., 1977; Hanify et al., 1981; Smith et al., 1982a), the report by the Department of Health is essentially anecdotal, involving two women who gave birth to malformed children (one with an atrial septal defect and a malformation of the tricuspid valve of the heart, and the other with biliary atresia). In both cases, exposure to 2,4,5-T could not be ruled out. Based on an analysis of spraying records, the time course of the pregnancies and plant damage near the women's homes, however, the Department of Health, New Zealand (1980) concluded that there was insufficient evidence to implicate 2,4,5-T spraying as a causative factor. Even if the spraying had been implicated, a lack of information on 2,3,7,8-TCDD levels in the spray and the absence of any monitoring data on 2,4,5-T or 2,3,7,8-TCDD would limit the usefulness of this report.

The study by McQueen et al. (1977) is not published in the open literature but is summarized by Milby et al. (1980). According to the summary, McQueen et al. (1977) "...examined the epidemiology of neural-tube defects in three areas in New Zealand and concluded 'there is no evidence to implicate 2,4,5-T as a causal factor in human birth defects.'" No additional details are provided.

Hanify et al. (1981) performed an epidemiologic study in Northland, New Zealand, in areas where spraying of 2,4,5-T was done by various companies for a number of years. The rate of birth defects was obtained from an examination of hospital records in seven nonoverlapping areas on a monthly basis over a period extending from 1959-1977. The rate of birth defects from 1959-1965 represented the rate for a nonexposed population since this was prior to the use of 2,4,5-T, while the incidence of birth defects from 1972-1976 represented the rate for the exposed population. During the time of the survey there were 37,751 births, 436 stillbirths, 264 deaths shortly after birth, and 510 congenital anomalies. Three categories of birth defects, heart abnormalities, hypospadias and epispadias, and talipes, had elevated rate ratios of >1 ($p=0.05$) in comparisons between the exposed (1972-1976) and control (1959-1965) populations. Exposure estimates were made for the seven areas and for different years using company records of aerial spraying and a model that factored in assumed fractional removal rates/month (this factor was assumed to be either 1.0 or 0.25). Comparisons of the rate of specific malformations with exposure demonstrated a statistically significant association between the occurrence of talipes and exposure when the fractional removal rate was assumed to be 0.25. There was, however, no statistically significant association where 1.0 was used as the fractional removal rate.

Smith et al. (1982a) investigated the outcome of pregnancy in families of professional 2,4,5-T applicators and agricultural contractors in New

Zealand. Agricultural contractors were chosen as the control population since both sprayers and contractors were of the same economic group with similar outdoor occupations. The survey was conducted by mail with 89% of the chemical applicators responding and 83% of the agricultural contractors responding to questions about their use of 2,4,5-T and its temporal relationship to reproductive histories regarding birth, miscarriages, stillbirths and congenital defects. The relative risks of congenital defects and miscarriages were 1.19 (0.58-2.45% confidence limits) and 0.89 (0.61-1.30% confidence limits) for the wives of chemical sprayers as compared with the wives of agricultural contractors. These data indicate that exposure of fathers and mothers (i.e., while cleaning clothes) had no effect on the outcome of pregnancy. Biases that may have affected the results (such as the age of the mother at childbirth, smoking habits and birth to Maori parents) were investigated and eliminated as possible confounders.

The two reports from Australia (Aldred, 1978; Field and Kerr, 1979) also present apparently conflicting results. The report by Aldred (1978) is not published in the open literature, but the following summary is taken from Milby et al. (1980): "The report concluded that birth defects in a group of babies born in the [Yarram] district in 1974 and 1976 could not be attributed to exposure to 2,4,5-T or 2,4-D." Additional details that might be useful in assessing the rationale for this statement are not provided in the summary. The report by Field and Kerr (1979) plotted the incidence of neural-tube defects (anencephaly and meningomyelocele) in New South Wales, Australia, over the years 1965-1975, and the usage of 2,4,5-T in all of Australia during the previous years. The authors noted a decrease in the incidence of neural-tube defects expected on the basis of the plotted line in 1975 and 1976, when Australia instituted monitoring of 2,4,5-T to ensure a 2,3,7,8-TCDD level <0.1 ppm. The data were not tested for significance; although Field and Kerr (1979) indicated that they consider the epidemiological data on neural-tube defects to be "relatively complete," they do not comment on the increasing incidence of neural-tube defects during the time period of this study and whether or not an increase in the thoroughness of reporting neural-tube defects could have contributed to the apparent correlation of 2,4,5-T exposure with these defects. A replotting of the data suggests that the incidence of cleft palate correlates better with 2,4,5-T usage than with time. Nonetheless, the appropriateness of correlating 2,4,5-T usage in all of Australia with the incidence of defects in one area of Australia is questionable.

Thomas (1980) used an approach similar to that of Field and Kerr (1979) on data from Hungary. One major difference, however, is that Thomas (1980) compared the incidence of stillbirths, cleft lip, cleft palate, spina bifida, anencephalus and cystic kidney disease in all of Hungary between 1976 and 1980 with 2,4,5-T use in 1975 in all of Hungary. Because Hungary requires compulsory notification of malformations diagnosed from birth to age 1 year, because a relatively large percentage (55%) of the Hungarian population lives in rural areas where 2,4,5-T exposure may be expected to be greatest, and because annual use of 2,4,5-T in Hungary had risen from 46,000 kg in 1969 to 1,200,000 kg in 1975, Thomas (1980) considered Hungary to be "...probably the best country in which to examine possible health effects of this herbicide." All indices of birth defect rates decreased or remained stable over the period of study.

In addition to contamination of 2,4,5-T being a potential source of 2,3,7,8-TCDD exposure, 2,3,7,8-TCDD is also an inadvertent contaminant of

2,4,5-trichlorophenol (TCP). Chronic exposure to 2,3,7,8-TCDD may occur during the manufacture of TCP and high level acute exposure to 2,3,7,8-TCDD has occurred after an accident in July, 1976 at the ICMESA TCP chemical factory in Seveso, Italy (Bonaccorsi et al., 1978). In this accident, the reaction used to produce TCP became uncontrolled, producing conditions favorable for 2,3,7,8-TCDD formation before venting the contents of the chemical reactor into the atmosphere. The resulting cloud of chemicals settled over a heavily populated area. Although the amount of 2,3,7,8-TCDD released was not known, the reported cases of chloracne, a symptom of acute exposure to 2,3,7,8-TCDD, indicated that exposure to 2,3,7,8-TCDD had occurred. Some preliminary results are available from epidemiologic studies of reproductive events in the inhabitants of Seveso, and recently a study has become available on the reproductive history of men employed in the chemical manufacturing industry with possible chronic exposure to 2,3,7,8-TCDD (Townsend et al., 1982).

Epidemiologic studies to determine the reproductive effects in individuals exposed to 2,3,7,8-TCDD and TCP following the accidental contamination of a populated area around Seveso, Italy, are not completed. The incidence of spontaneous abortions occurring between March 1976 and January 1978 have been reported for inhabitants in the area around Seveso by Bonaccorsi et al. (1978), Reggiani (1980) and Bisanti et al. (1980). The spontaneous abortion rate in the contaminated area for the three trimesters following the accident was 13.1, 11.0 and 13.05%, which was similar to the worldwide 15-20% frequency of spontaneous abortion. Subdividing the contaminated area into highly, moderately, and least contaminated, and examining the rates for each area individually, also failed to demonstrate any change in the spontaneous abortion rate. The incidence rates of malformations also were examined; however, the numbers were too few for meaningful assessment. There are several inadequacies in these studies that might make them insensitive in detecting reproductive effects. The authors noted that there are many difficulties in interpreting these data. Adequate data on the incidence rates of spontaneous abortions and birth defects were not adequately available for the region before the accident as a result of suspected under-reporting. There was inadequate reporting even after the accident because of political turmoil with regard to the management of health services. Also, an unknown number of pregnancies were surgically aborted for fear of 2,3,7,8-TCDD-induced birth defects. In a recent review of the progress of epidemiologic investigations of the Seveso accident, Tognoni and Bonaccorsi (1982) indicated that the data on spontaneous abortions and malformation rates still needed verification, and that these data were too preliminary to allow for conclusions.

Townsend et al. (1982) investigated the reproductive history of wives of employees potentially exposed to 2,3,7,8-TCDD during chlorophenol production in Midland, MI. A total of 930 potentially exposed males were identified who had worked for ≥1 month between January 1939 and December 1975 in a job with potential 2,3,7,8-TCDD exposure. Exposure estimates of low, moderate and high were made by an industrial hygienist primarily from job description and surface contamination data; however, the high potential exposure group was reserved for process workers during 1963-1964 when changes in operations resulted in a number of cases of chloracne. The control population was an equal number of male employees not involved in any process that might involve exposure to 2,3,7,8-TCDD and matched for date of hire. In these groups, 586 wives were identified and 370 agreed to participate as the exposed group, while 345 wives of a potential control group of 559 agreed to participate. After identification of the participants, a personal interview was conducted with the wives to determine pregnancy outcome. Of the total of 737 conceptions in the exposed category and 1785 conceptions in the control category (conceptions that occurred in the exposed group before work records indicating potential exposure to 2,3,7,8-TCDD were placed in the control group), there was no statistically significant increase in spontaneous abortions, stillbirths, infant deaths or selected congenital malformations. Sample sizes were too small to provide meaningful data if the populations were subdivided by extent of exposure. The authors suggested that many confounding factors could account for these negative results, such as the inappropriate selection of the populations, the use of "exposed" persons in both exposed and control groups, unidentified covariables and low power; however, it was asserted that these results were consistent with animal data, which report that paternal exposure to 2,3,7,8-TCDD does not affect the conceptus.

Poole (1983), in testimony before the House Committee on Science and Technology, described a reanalysis of the primary data used by Townsend et al. (1982). In this reanalysis, the relative risk of cleft palate and cleft lip were reported to be 1.9 (90% confidence intervals of 1.0-3.6) in the years 1971-1974 for both the control and exposed groups (the comparison population was not described). At the same House Committee hearing, Houk (1983) presented data from the Birth Defect Monitoring Program of the Centers for Disease Control on the yearly rate of cleft palate alone or cleft lip with or without cleft palate for births in Midland County, Michigan (the site of Dow Chemical Company's chlorophenol production facility) during the years 1970-1981. The data indicated an increased rate for these defects of between 50 and 100% in the years 1971-1975, with the rate returning to normal from 1976-1981. The observed increase was statistically significant if the rates for cleft palate alone and cleft lip with or without cleft palate were combined; however, it was the opinion of Houk (1983) that these defects should not be combined since the causal mechanism may be different. The Michigan Department of Public Health (1983a) also reported these results and, in addition, demonstrated that the same results occurred if the comparison was made with other counties in Michigan as well as with the general population of the United States. It was noted in this report that "runs" of increases in oral cleft for successive years have occurred in six other counties with no obvious chemical exposure. The Michigan Department of Public Health (1983a) interpreted the data to indicate that a more detailed case control study was necessary to determine if any common factors may exist, such as exposure to chemicals contaminated with 2,3,7,8-TCDD.

A similar but limited study of the reproductive history of the wives of employees of the Long Island Railroad was performed by Honchar for NIOSH (1982). The employees were concerned about the use of 2,4,5-T for maintenance along the right-of-way. There were 170 live births as indicated by union files during the study period from 1975-1979. For each birth, insurance claims were reviewed to determine any health problems during the first year of life. The incidence of major birth defects was underrepresented in the study population when compared with data from the Metropolitan Atlanta Congenital Defects Program (3 observed and 3.81 expected). Some minor health problems (i.e., tear duct obstruction) were elevated; however, the authors considered this to have resulted from diagnostic bias. It was concluded that no association between birth defects and exposure to 2,4,5-T was demonstrated in this study.

To test any possible association between birth defects and exposure to Agent Orange in Vietnam veterans, Erickson et al. (1984) conducted a case-control study on newborns with various types of congenital defects in the metropolitan Atlanta area during the years 1968 through 1980. Though most of the Vietnam veterans received from the Army Agent Orange Task Force an estimated opportunity index score regarding their exposure to Agent Orange, 25% of the Vietnam veterans interviewed in this study felt that they were exposed and approximately an equal proportion did not know if they were exposed to Agent Orange. Increased estimated risks for fathering babies with 1) spina bifida, 2) cleft lip with or without cleft palate and 3) certain tumors were found in this study. However, the authors concluded that "Vietnam veterans who had greater estimated opportunity for Agent Orange exposure did not seem to be at a greater risk for fathering babies with all types of defects combined" (Erickson et al., 1984).

Summary

Carcinogenicity. By adding together the number of workers exposed to phenoxy acids and/or chlorophenols from all case studies, an unusually high number of STSs is shown, considering the rarity of the disease. This excess is suggestive of an association of cancer with exposure to phenoxy acids and/or chlorophenols, and consequently, with the impurities found in these herbicides, including 2,3,7,8-TCDD.

Two Swedish case-control studies report highly significant association of STS with exposure to phenoxy acid and/or chlorophenols. They do not pinpoint the risk to the dioxin contaminants, however. In fact, in one study, the risk was found to extend to phenoxy acids free of dioxin impurities. In that study, the risk increases to 17 when phenoxy acids known to contain dioxin impurities (polychlorinated dibenzodioxins and dibenzofurans) are considered. The extent of possible observer bias and recall bias introduced into these studies by using self-administered questionnaires is not of sufficient magnitude to have produced the highly significant risks found in the studies.

Later studies did not reveal a significant excess risk of STS. However, methodology problems make these latter studies limited with respect to evaluating the risk of STSs from exposure to phenoxy acids and/or chlorophenols and, consequently, 2,3,7,8-TCDD.

The Swedish case-control studies provide limited evidence for the carcinogenicity of phenoxy acids and/or chlorophenols in humans. However, with respect to the dioxin impurities contained therein, the evidence for the human carcinogenicity for 2,3,7,8-TCDD based on the epidemiologic studies is only suggestive because of the difficulty of evaluating the risk of 2,3,7,8-TCDD exposure in the presence of the confounding effects of phenoxy acids and/or chlorophenol.

There is less evidence incriminating 2,4,5-T and/or 2,3,7,8-TCDD as the cause of malignant lymphoma and stomach cancer in humans.

Teratogenicity and Reproductive Effects. A number of studies, mostly correlation studies, have been conducted on groups of persons exposed to 2,3,7,8-TCDD as a contaminant of the herbicides 2,4,5-T, 2,3,5-TP or the chemical of TCP. Although some studies have shown a positive association between exposure to 2,4,5-T, 2,4,5-TP and birth defects or abortions, other studies have not. In these studies, exposure was always mixed, with 2,3,7,8-TCDD being only a minor component. Hence, it is not possible to attribute with certainty any positive finding to 2,3,7,8-TCDD. It is possible, since levels of 2,3,7,8- TCDD contamination of 2,4,5-T, 2,4,5-TP and TCP were only estimated, that the negative results reflect the exposure was too low or the study designs too insensitive to elicit a detectable response. From an extensive review of dioxin-induced animal and human reproductive toxicity data by Mattison et al. (1984) and another review of 15 reports dealing with human exposure to dioxins and reproductive effects by Hatch (1984), it can be concluded that epidemiologic observations from well designed studies are warranted before deriving any conclusion on dioxin-induced reproductive toxicity in humans.

VII. MECHANISMS OF TOXICITY

Pertinent data regarding the mechanisms of toxicity of 2,4,5-TP could not be located in the available literature. However, the following studies might reflect on the mechanisms of toxicity of 2,4,5-TP.

Hiltibran (1975) found that 2,4,5-TP alters the oxygen and phosphate uptake by bluegill (Lepomis macrochirus) liver mitochondria in the presence of succinate or α-ketoglutarate as the mode of its toxic action. Oxygen uptake in this case was inhibited more than by 2,4,5-T or 2,4-D. However, in the absence of succinate or α-ketoglutarate, 2,4,5-TP affected oxygen uptake less than 2,4,5-T.

Venkaiah and Patwardhan (1978) observed that 2,4,5-TP affected the rat liver mitochondrial energy transfer by inhibiting mitochondrial phosphorylation, and active ion uptake. 2,4,5-TP was also found to contract the swollen mitochondria by adenosine triphosphate.

Summary

The results from these two studies indicate that 2,4,5-TP-induced toxic effects may be mediated through alteration of the oxygen and phosphate uptake reflecting inhibition of mitochondrial energy transfer process. However, much more work needs to be done before any conclusion can be derived regarding the mechanism of 2,4,5-TP-induced toxicity.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = \underline{\quad\quad} \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner, the U.S. EPA (1986) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]
- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]
- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]
- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell\text{/day}} = \_\_\_\_ \text{ mg}/\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (\_\_\_ \ \ell\text{/day})} = \_\_\_\_ \text{ mg}/\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Contamination of 2,4,5-TP with 2,3,7,8-TCDD may have been responsible for some of the biological effects reported herein. Most of the data have been obtained from the summaries of the health effects data published by Dow Chemical Company and they did not report the extent of contamination of the product. However, it is known that for registration of the product with the U.S. EPA 2,4,5-TP is required to have <0.1 ppm 2,3,7,8-TCDD as a contaminant.

The summary data indicate single dose oral LD_{50}s for 2,4,5-TP range from 600-1000 mg/kg bw for mice, rats, guinea pigs and rabbits for acid and ester formulations; for the acid, an LD_{50} of 650 mg/kg was determined in rats (Rowe and Hymas, 1954). Gross general symptoms of intoxication include depression, posterior quarter muscle weakness, irritation of the stomach and minor liver and kidney damage.

2,4,5-TP appears to be more toxic than 2,4,5-T in rats when administered orally over a prolonged period. Oral administration of 5 mg/kg bw/day of 2,4,5-TP to rats for 90 days in the diet produced histopathologic changes in the liver and kidney (Dow Chemical Company, 1962), whereas a dose of 2 mg/kg bw/day was reported to be a NOEL in dogs (parameters measured were not reported in NRCC, 1978) (Dow Chemical Company, 1963).

The only information available on the chronic toxicity of 2,4,5-TP (other than oncogenic study) comes from unpublished investigations in rats and dogs conducted by Dow Chemical Company. A 2-year dietary regimen of a potassium salt of 2,4,5-TP (0, 0.26, 0.8, 2.6 or 7.9 mg a.e./kg bw/day) only revealed a significant increase in relative kidney:body weight ratios in male rats at all doses and decreased body weight in male rats at the highest dose (Gehring and Betso, 1978). Due to the absence of morphological alterations in the kidney at any dose level, these investigators felt that the increase in kidney weight reflected a physiological adaptation rather than an untoward effect (Gehring and Betso, 1978).

Evidence of adverse effects on the livers of male dogs, however, was observed at 2.6 mg a.e./kg bw/day 2,4,5-TP. Both male and female dogs were affected at doses of 8.2 and 9.9 mg a.e./kg bw/day, respectively (Gehring and Betso, 1978). This 2-year feeding study of 2,4,5-TP resulted in mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation in females, accompanied by elevations of SGOT and SGPT levels. A 0.9 mg a.e./kg bw/day was judged to be a NOAEL for the male dog and 2.6 mg/kg/day for female dogs.

In addition to limited information from classical toxicological studies (such as acute, short-term or chronic) little information is available concerning the teratogenic potential of 2,4,5-TP. Two studies have been encountered on the potential teratogenic activity of 2,4,5-TP. Courtney (1977) administered 2,4,5-TP to pregnant CD-1 mice at a dose level of 1.5 mM/kg/day (398 mg/kg/day) on days 12 through 15 of gestation. The compound was administered both by gavage using corn oil:acetone (9:1) as the vehicle and by s.c. injection using DMSO as the vehicle. Both administrations caused a significant ($p<0.01$) increase in maternal weight, probably due to increased liver weight, and a significant increase ($p<0.01$) in maternal liver-to-body weight ratios. Both routes of exposure were also associated with a significant ($p<0.01$) decrease in fetal weight. Oral and s.c. exposures to 2,4,5-TP were associated with respective 7 and 3% incidences of cleft palate in total fetuses.

The other study on the teratogenicity of 2,4,5-TP is an unpublished study by Dow Chemical Company, summarized in U.S. EPA (1979a). Because the summary is so brief, it is reproduced in full below:

> Dow Chemical Company studied the reproductive effects of silvex and the propylene glycol butyl ether ester of silvex (silvex-PGBE), each containing <0.5 ppm TCDD. Sprague-Dawley rats were exposed to 25-100 mg/kg of silvex on days 6-15 of gestation. Significant effects on fetal mortality and birth weight were observed in the litters of treated dams. Skeletal anomalies, such as cleft palate, retarded ossification and extra cervical ribs were observed among the exposed fetuses. Micropthalmia (abnormal smallness of the eyeball) and cardiovascular abnormalities were also seen. Similar effects were observed when animals were dosed with silvex-PGBE, or when dosed for three-day intervals during the period of early organogenesis.

Quantification of Noncarcinogenic Effects

Derivation of 1-Day HA. The available data are inadequate to derive a 1-day HA. No quantitative data on acute exposure of humans to 2,4,5-TP were available. All information on single oral exposure of laboratory animals is concerned with lethality. The oral LD_{50}s range from ~600-650 mg/kg in the rats; 750-819 mg/kg in rabbits; 1250 mg/kg in guinea pigs and 1410 mg/kg in mice for acid and ester formulations (Rowe and Hymas, 1954). General symptoms of acute toxicity include muscle weakness, irritation of the stomach and minor damage to the liver and kidney. Due to the lack of suitable data to derive the 1-day HA, it is recommended that the 10-day HA be used as a conservative estimate.

Derivation of 10-Day HA. There is concern that 2,4,5-TP might be a teratogen since there is evidence that a similar herbicide, 2,4,5-T, is a teratogen; however, little information is available on the teratogenic or reproductive effects of 2,4,5-TP or its esters, and the available data are inadequate for determining a 10-day HA using teratogenicity as an endpoint. Only two animal teratogenicity studies have been conducted. These two studies involved oral administration of 2,4,5-TP or the propylene glycol butyl ether ester of 2,4,5-TP during gestation: the first in CD-1 mice (Courtney, 1977) and the second in Sprague-Dawley rats (U.S. EPA, 1979a). The only dose tested in mice by the oral route, ~389 mg/kg/day on days 12 through 15 of gestation, produced cleft palate in 7% of the exposed fetuses as compared with 0% in the controls. In rats, the lowest dose tested, 25 mg/kg/day on days 6-15 of gestation, also resulted in a significant increase in cleft palate as well as retarded ossification, other skeletal anomalies and increased fetal death. Although it appears that 2,4,5-TP is somewhat less potent than 2,4,5-T, the complex pattern of dose and dose schedule on the apparent activity of these compounds (Courtney, 1977) precludes use of data on 2,4,5-T to derive a 10-day HA for 2,4,5-TP by analogy.

Two unpublished studies by Dow Chemical (1962, 1963) that described the toxicity of 2,4,5-TP to rats and dogs were located. No effects were reported in dogs administered 2 mg/kg/day 2,4,5-TP in the diet for 89 days. Only one dose level was employed in this study, and the available description of this unpublished work provided no detail on the extensiveness of pathologic examination. In a companion study, rats administered 5 mg/kg/day of the sodium salt or PGBE ester of 2,4,5-TP for 90 days had an increase in relative weight of the liver and kidney with "histopathologic changes" in both.

Of these two studies, the study using the dog that identified a NOEL of 2 mg/kg should preferentially be used to calculate a 10-day HA. The calculations for a 10 kg child consuming 1 ℓ of water/day is given below:

For a 10 kg child:

$$\frac{2\text{ mg/kg/day} \times 10\text{ kg}}{1\ \ell\text{/day} \times 100} = 0.2\text{ mg/}\ell$$

where:

2 mg/kg/day = no observed effect level in dogs (Dow Chemical, 1963)
10 kg = assumed average weight of a child
1 ℓ/day = assumed consumption of drinking water by a child
100 = uncertainty factor, 10 to account for interspecies variability and 10 to account for intraspecies variability

Longer-term Health Advisory. No information was found in the available literature that was suitable for determination of the longer-term HA value for 2,4,5-TP. It is therefore recommended that the DWEL, adjusted less potent than 2,4,5-T, the complex pattern of dose and dose schedule on the apparent activity of these compounds (Courtney, 1977) precludes use of data on 2,4,5-T to derive a 10-day HA for 2,4,5-TP by analogy.

Two unpublished studies by Dow Chemical (1962, 1963) that described the toxicity of 2,4,5-TP to rats and dogs were located. No effects were reported in dogs administered 2 mg/kg/day 2,4,5-TP in the diet for 89 days. Only one dose level was employed in this study, and the available description of this unpublished work provided no detail on the extensiveness of pathologic examination. In a companion study, rats administered 5 mg/kg/day of the sodium salt or PGBE ester of 2,4,5-TP for 90 days had an increase in relative weight of the liver and kidney with "histopathologic changes" in both.

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where:

2 mg/kg/day = no observed effect level in dogs (Dow Chemical, 1963)
10 kg = assumed average weight of a child
1 ℓ/day = assumed consumption of drinking water by a child
100 = uncertainty factor, 10 to account for interspecies variability and 10 to account for intraspecies variability

Longer-term Health Advisory. No information was found in the available literature that was suitable for determination of the longer-term HA value for 2,4,5-TP. It is therefore recommended that the DWEL, adjusted for a 10-kg child (0.08 mg/ℓ) be used as a conservative estimate of a longer-term HA, for a child and that the DWEL be used directly as a conservative estimate for the longer-term HA for an adult.

Assessment of Lifetime Exposure and Derivation of a DWEL. Lifetime DWELs are normally derived from 2-year feeding studies in animals. The animal species that is most sensitive to the toxic effects or the species that metabolizes the compound in a manner similar to that in man is selected for estimating RfDs for humans. In these studies, a NOAEL or LOAEL is identified. This level is divided by an uncertainty factor(s), which may vary from 10-1000 based on the overall scientific judgment to determine an RfD.

In 1976, the U.S. EPA, Office of Drinking Water established an interim primary drinking water standard of 0.01 mg/ℓ. This was based on a Dow Chemical Company study on dogs. In this study, a NOEL of 0.9 mg/kg was divided by an uncertainty factor of 500 and a final standard of 0.01 mg/ℓ was calculated for a 70 kg adult consuming 2 ℓ of water/day. This standard is 20% of the total ADI.

The NAS (1977) recommended a concentration of 0.00525 mg/ℓ 2,4,5-TP in drinking water, based on an ADI of 0.0525 mg/day (or 0.00075 mg/kg/day) and 2 ℓ of water/day assuming that 20% of the total ADI comes from drinking water. This recommendation was based on a 2-year study reported by Mullison (1966) on dogs. The NAS calculated the ADI value from a NOAEL of 0.75 mg/kg/day and a 1000-fold uncertainty factor.

Limited chronic oral toxicity data are available for 2,4,5-TP to derive an RfD. For example, Mullison (1966) and Gehring and Betso (1978) reported a study in which groups of four male and four female dogs received Kurosal SL, containing the potassium salt of silvex equivalent to approximately 53% of the acid form of silvex, at dietary levels equivalent to doses of 0, 0.9, 2.6 and 9.9 mg/kg/day for females and 0, 0.9 and 2.6 mg/kg/day for males for 2 years. The parameters monitored in this study included weekly body weight, food consumption, hematology, serum biochemistry and histopathology of target organs. The only observed adverse effects were dose-related histopathological changes in the livers of female dogs receiving 9.9 mg/kg/day and in males receiving 2.6 mg/kg/day. No adverse effects on growth, food consumption, hematological parameters, or other tissues were observed. Thus, 0.9 mg/kg/day was the NOAEL. However, the Agency considers (RfD verification meeting notes of 1/6/87) the authors' claim that the dose of 0.9 mg/kg/day is incorrect. Instead, the Agency considers the estimation of NOAEL should be 0.75 mg/kg/day based on a different exposure assumption. Based on previous guidelines (U.S. EPA, 1987) it appears that the most appropriate dose level from which to estimate an RfD would be this male dog NOAEL of 0.75 mg/kg bw/day (diet adjusted from 0.9 mg/kg) (Mullison, 1966), since it represents the highest exposure level that produced no signs of toxicity in what appears to be a more sensitive species than the rat. The results of this study are confirmed by Gehring and Betso (1978). By applying an uncertainty factor of 100 to 0.75 mg/kg/day (NOAEL), an RfD of 0.008 mg/kg/day is derived. This uncertainty factor is appropriate for extrapolating from an animal NOAEL; it is designed to protect the most sensitive members of the human population and to allow for possible differences in the sensitivity between species in extrapolating from an animal study to humans.

$$\text{RfD} = \frac{\underline{0.75\ \text{mg/kg/day}}}{100} = 0.0075\ \text{mg/kg/day}\ (\sim 0.008\ \text{mg/kg/day})$$

where

0.75 mg/kg/day = NOAEL adjusted from Mullison (1966)

100 = uncertainty factor, 10 to account for interspecies variability and 10 to account for intraspecies variability

A lifetime DWEL of 0.28 mg/ℓ for an adult can be calculated by multiplying the RfD by the assumed body weight of an adult (70 kg) and dividing by the assumed consumption of 2 ℓ of water/day.

$$\text{DWEL} = \frac{0.75 \text{ mg/kg/day} \times 70 \text{ kg}}{2\ \ell\text{/day}} = 0.26 \text{ mg/}\ell$$

Summary

The 1-day, 10-day, longer-term and lifetime HAs calculated for 2,4,5-TP are summarized in Table VIII-1. The data demonstrate that as the length of exposure increases, the recommended "safe" dose levels for a child or adult decreases. These dose levels derived from data on experimental animals are designed to protect the most sensitive members of a population from chronic and short-term exposure to 2,4,5-TP in drinking water.

Carcinogenic Effects

The available carcinogenicity studies are inadequate to properly assess the human carcinogenic potential of 2,4,5-TP. The studies all suffer from one or more of the following deficiencies: single dose only, too few animals or less than lifetime of dosing. The studies all show no significant increase in tumors. According to the U.S. EPA (1986) Guidelines for Carcinogen Risk Assessment, 2,4,5-TP is classified in Group D, meaning that the available data is considered to be inadequate to evaluate its carcino-

TABLE VIII-1

Summary of Calculated Health Advisories for 2,4,5-TP

Health Advisory	NOEL or NOAEL	Species/ Route	Effect	Calculated Level for Safe Exposure		Reference
				Child	Adult	
1-Day	No available data[a]					
10-Day	2 mg/kg/day (NOEL)	dog/ diet	histopathological effects in kidney and liver at higher doses	0.2 mg/ℓ (0.2 mg/day)		Dow Chemical Co., 1963
Longer-term	No available data[b]					
Lifetime DWEL	0.75 mg/kg/day* (NOAEL)	dog/ diet	mild hepatocyte necrosis in males at higher doses	NA	0.26 mg/ℓ (0.52 mg/day)	Mullison, 1966

*As calculated by the NAS and accepted by the Office of Pesticides Programs of the U.S. EPA.

NA = Not applicable

[a] Recommended that the 10-day HA be used as a conservatve estimate.

[b] Recommended that the DWEL adjusted for a 10 kg child be used as a conservative estimate for the longer term HA for a child and that the DWEL be used directly as a conservative estimate of the longer term HA for an adult:

$$\text{longer-term HA (child)} = \frac{0.75 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \ \ell\text{/day} \times 100} = 0.07 \text{ mg/}\ell$$

$$\text{longer-term HA (adult)} = \text{DWEL} = 0.26 \text{ mg/}\ell$$

genic potential. However, information that 2,4,5-TP is probably contaminated with 2,3,7,8-TCDD gives reason to be very concerned about its exposure. Given the known or suspected presence of 2,4,5-TP, precautions should be taken to insure that there is no meaningful exposure to 2,3,7,8-TCDD.

As a manufactured product, there is reason to consider 2,4,5-TP with a hazardous level of 2,3,7,8-TCDD as a contaminant as an EPA Group B2 compound, meaning it is probably carcinogenic for humans. Because of the variations in ambient environmental conditions, a case-by-case evaluation will have to be performed to determine the nature of possible carcinogenic hazard to 2,4,5-TP.

Existing Guidelines, Standards and Recommendations for 2,4,5-T and 2,4,5-TP

The U.S. EPA has taken significant regulatory action on 2,4,5-TP as a herbicide product. As of February 1987 the result of the actions taken should be to reduce the availability of 2,4,5-TP and hence its discharge to the environment to virtually a nil level. The exception to this would be a situation where storage of 2,4,5-TP in controlled or uncontrolled dump sites or related scenarios might result in a discharge to the environment. The regulatory action against herbicide uses began in February 1979 when 2,4,5-TP use in foresty, rights of way, pasture, home and garden, and ornamental gardening was suspended (U.S. EPA 1979c). Between 1979 and February 1985 all other registrations for 2,4,5-TP uses were cancelled by the U.S. EPA. From February 1985 through February 1986, existing 2,4,5-TP stockpiles only were allowed into commerce for highly limited use. As of February 1986 all sale of 2,4,5-TP ceased.

The National Interim Primary Drinking Water Regulations (U.S. EPA, 1979a) allows up to 10 ppb of 2,4,5-TP in drinking water.

The National Academy of Sciences (NAS, 1977) has suggested an ADI for humans of 0.00075 mg/kg/day for 2,4,5-TP based on a NOAEL of 0.75 mg/kg/day and a 1000-fold uncertainty factor. The NOAEL was estimated from a 2-year feeding study performed by Mullison (1966) on the dog. NAS (1977) has suggested a NOAEL for 2,4,5-TP in drinking water of 0.00525 mg/ℓ, assuming that 20% of the total ADI comes from this source and 2 ℓ of contaminated water are consumed/day.

Special Groups at Risk

There is insufficient data on 2,4,5-TP to define high risk subpopulations, or the effects of simultaneous exposure to 2,4,5-TP and other pollutants.

Exposure to high levels of 2,4,5-TP would most likely occur during the manufacturing and formulating processes, during spray operations for weed control, or in forestry and rangeland operations. The other major group at risk from reproductive and teratogenic effects are women of child-bearing age who are employed in such occupations as foresters, pesticide applicators, highway construction and maintenance equipment operators. Precautions should be exercised in such operations to the greatest possible extent.

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